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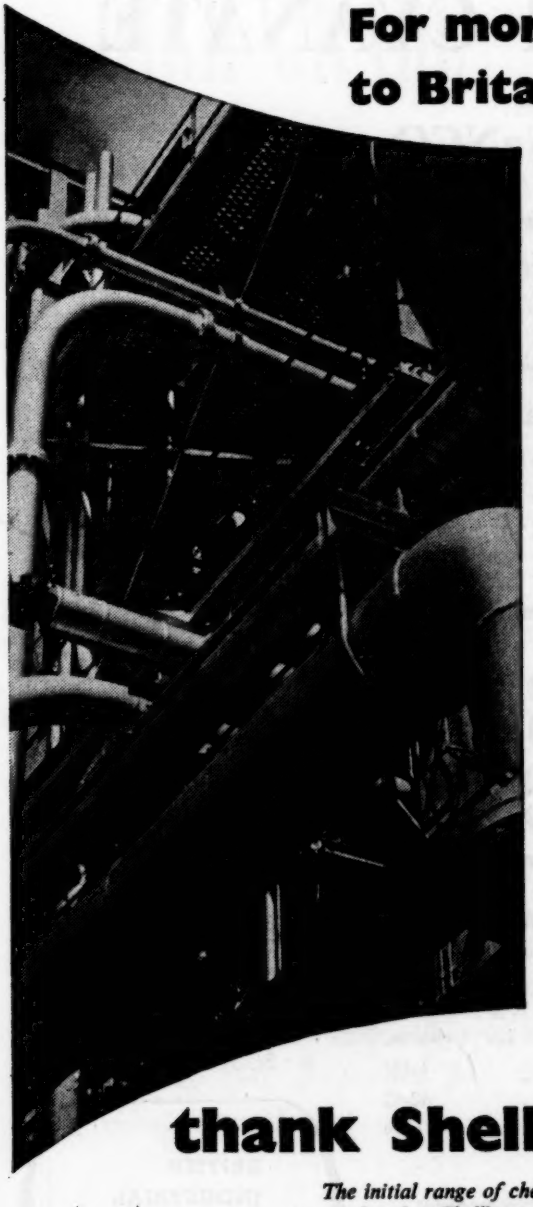

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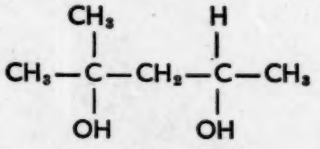

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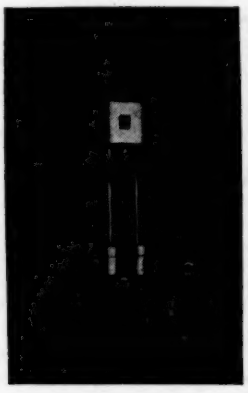

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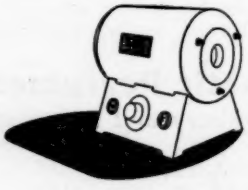

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9. New compounds should be indicated by underlining the name at its first mention (excluding headings) both in the introduction and in the experimental section, and by giving analytical results in the form: " Found: ———. ——— requires ———." Analytical results for compounds which have previously been adequately described in the literature should be given in the form: " Found: ———. Calc. for ———: ———."

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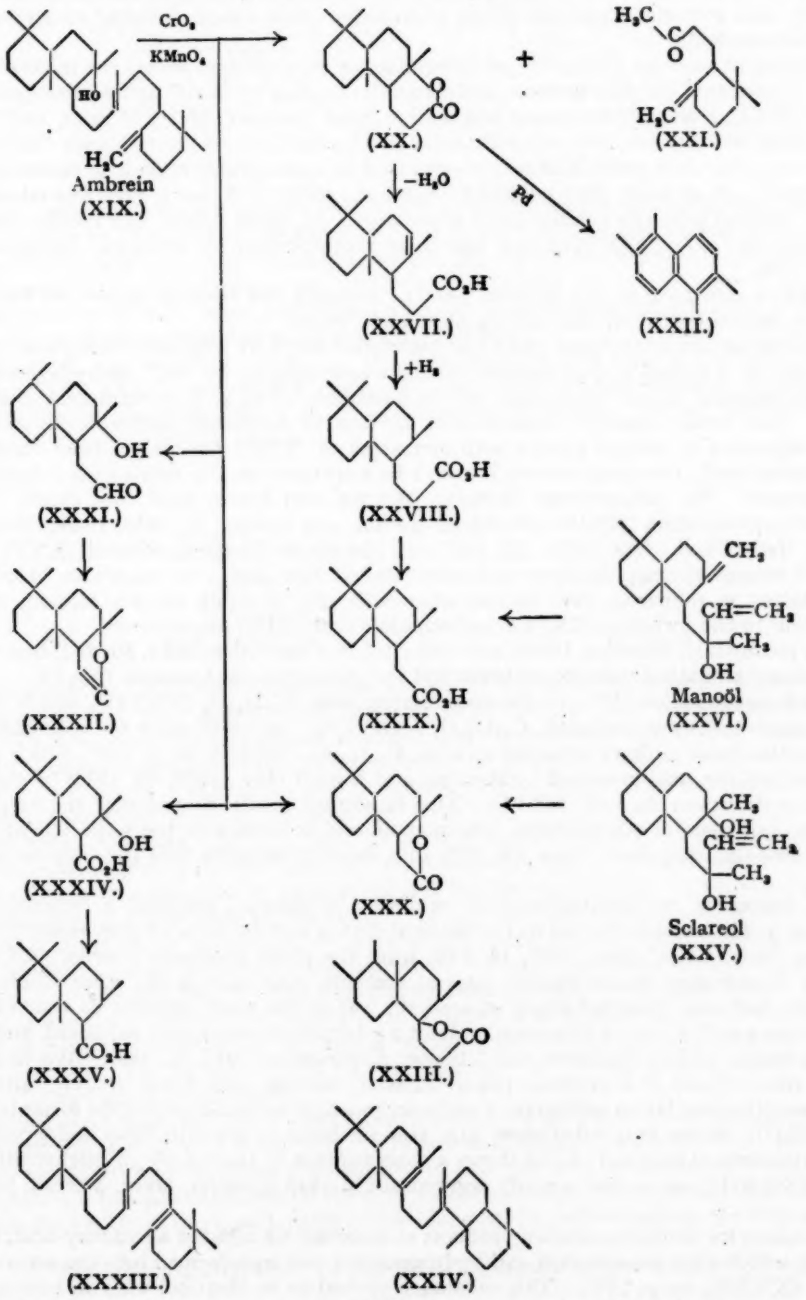
acid oxidation of coprostanone was also isolated from ambergris. The recent paper of Turfitt (*Biochem. J.*, 1948, **42**, 376) on the microbial oxidation of steroids indicates that this dicarboxylic acid may be formed in the intestine of the sperm whale by microbial oxidation of coprostanone.



Ambrein. In 1820, Pelletier and Caventou (*J. Pharm.*, 1820, **6**, 49) isolated from ambergris a colourless crystalline substance which they called ambrein. Suzuki (*Jap. J. Med. Sci. Trans.*, 1925, II, **1**, 31) was the first to prepare it in a pure state (m. p. 83°). In 1946, two simultaneous publications established the chemical structure of this substance as being a tricyclic triterpene

alcohol, $C_{30}H_{52}O$, containing one tertiary hydroxyl group and two double bonds (Ruzicka and Lardon, *Helv. Chim. Acta*, 1946, **29**, 912; Lederer, Marx, Mercier, and Pérot, *loc. cit.*). Ambrein is thus the first tricyclic triterpene and a representative of the small group of animal triterpenes (see above). The study of its structure has led to results of general interest and has proceeded so rapidly that it is the first of all cyclic triterpenes whose exact chemical structure has been entirely established.

Oxidation of ambrein (XIX) by permanganate or chromic acid severs the molecule into two pieces: a saturated bicyclic lactone [ambreinolide, $C_{17}H_{28}O_2$, (XX)] and a monocyclic ketone, $C_{13}H_{22}O$ (XXI), which still contains one double bond (Lederer, Marx, Mercier, and Pérot, *loc. cit.*; Ruzicka and Lardon, *loc. cit.*). Ruzicka and Lardon (*loc. cit.*) have shown that the double bond is exocyclic—in a methylene group—and that its hydrogenation leads to tetrahydroionone. The ketone $C_{13}H_{22}O$ must thus be dihydro-γ-ionone (XXI); it has a very fine odour and has also been isolated from the volatile parts of ambergris (Ruzicka, Seidel, and Pfeiffer, *Helv. Chim. Acta*, 1948, **31**, 827). The synthesis has been accomplished by Ruzicka, Büchi, and Jeger (*ibid.*, p. 293).

The exact structure of the bicyclic part of ambrein has become known as the result of researches carried out simultaneously in Zürich and Paris.

Dehydrogenation of ambrein (XIX) or ambreinolide (XX) with selenium gives 1 : 5 : 6-trimethyl- and 1 : 6-dimethyl-naphthalene (Ruzicka and Lardon, *loc. cit.*); dehydrogenation with palladium–charcoal in our laboratory led to formation of 1 : 2 : 5 : 6-tetramethylnaphthalene (XXII). This result induced Ruzicka and Lardon to formulate ambreinolide as (XXIII), because migration of methyl groups with formation of (XXII) had as yet been observed only with hydroxylated triterpenes where it could be explained as the result of a retropinacolinic rearrangement. We showed later (Lederer, Mercier, and Pérot, *Bull. Soc. chim.*, 1947, 345) that *quadricyclo*squalene (XXIV) (Heilbron, Kamm, and Owens, *J.*, 1926, 1630; Ruzicka and Hosking, *Helv. Chim. Acta*, 1931, **14**, 203) and the plant diterpene sclareol (XXV) also give 1 : 2 : 5 : 6-tetramethylnaphthalene with our catalyst [Pd (15%) on vegetable charcoal; the usual catalyst is prepared with animal charcoal]. As a result of this finding, there was no objection to the formulæ (XX) for ambreinolide and (XIX) for ambrein.

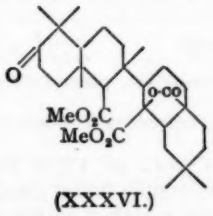
In the meanwhile, Ruzicka, Dürst, and Jeger (*Helv. Chim. Acta*, 1947, **30**, 353) had succeeded in establishing a relation between ambrein and the plant diterpene manoöl (XXVI). They had dehydrated ambreinolide (XX) to the unsaturated acid, $C_{17}H_{26}O_2$ (XXVII), which on hydrogenation gave the saturated acid, $C_{17}H_{28}O_2$ (XXVIII); on shortening the side-chain of this substance, the Swiss authors obtained an acid, $C_{16}H_{26}O_2$ (XXIX), m. p. 126°, which proved to be identical with an acid prepared by Hosking and Brandt (*Ber.*, 1935, **68**, 1311) by degradation of the plant diterpene manoöl (XXVI). This important result showed that the bicyclic parts of ambrein and manoöl are identical. As manoöl and sclareol give the same trihydrochloride (Hosking and Brandt, *Ber.*, 1935, **68**, 37), this identity includes also the bicyclic system of sclareol.

Soon afterwards, we isolated another oxidation product of ambrein, a lactone, $C_{16}H_{26}O_2$ (XXX), m. p. 121°, which proved to be identical with a lactone isolated previously by Ruzicka and Janot (*Helv. Chim. Acta*, 1931, **14**, 645) from the plant diterpene sclareol (XXV). This confirmed the identity of the bicyclic part of ambrein with that of the plant diterpenes and proved also that the hydroxyl group of ambrein was in the same position as that of sclareol. Ambreinolide was therefore a δ-lactone, and not a γ-lactone as previously supposed, and ambrein has the formula (XIX) (Lederer and Mercier, *Experientia*, 1947, **3**, 188). We had already proposed this formula in a previous paper (Lederer, Mercier, and Pérot, *loc. cit.*) after having isolated two other oxidation products of ambrein to which we had ascribed the formulæ (XXXI) and (XXXII); these two substances can also be isolated directly from ambergris.* The definitive formula of ambrein (XIX) shows a close relation to that of the (hypothetical) *tricyclo*squalene (XXXIII), as we had already pointed out in 1946 (Lederer, Marx, Mercier, and Pérot, *loc. cit.*).

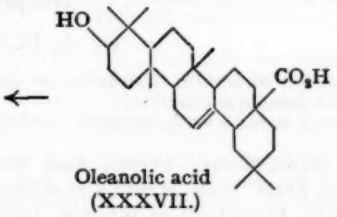
In searching for further oxidation products of ambrein, we isolated a hydroxy-acid, $C_{15}H_{26}O_3$ (XXXIV), which after dehydration and hydrogenation was transformed into the saturated acid, $C_{15}H_{26}O_2$ (XXXV), m. p. 135°. This substance proved to be identical with an acid isolated in Zürich by pyrolysis of the degradation product (XXXVI) of oleanolic acid (XXXVII), the most common pentacyclic triterpene acid derived from β-amyrin (Ruzicka, Gutmann, Jeger, and Lederer, *Helv. Chim. Acta*, 1948, **31**, 1746).

* The hydroxyl group in the formulæ for ambrein and ambreinolide had been until then placed at the carbon atom carrying the side-chain, and not on that carrying the methyl group.

As the bicylic part of ambrein had already been shown to be identical with the corresponding part of sclareol (XXV) and manoöl (XXVI) (see above), and as Jeger, Dürst, and Büchi (*Helv.*



(XXXVI.)

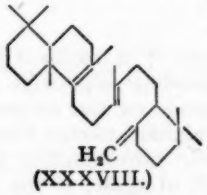


Oleanolic acid
(XXXVII.)

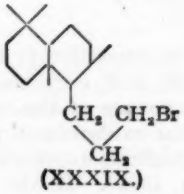
Chim. Acta, 1947, **30**, 1853) had proved the identity of the bicyclic system of the manoöl–sclareol group with that of the tricyclic diterpenes of the abietic acid group,* we thus come to the conclusion that structure and configuration of the bicyclic system of all these groups (plant diterpenes, plant triterpenes, and ambrein) is identical.

Quite recently, Meisels, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1949, **32**, 1075) have isolated the same C_{15} acid from degradation products of α-amyrin.

Dürst, Jeger, and Ruzicka (*ibid.*, p. 46) have recently described a partial synthesis of ambratriene (XXXVIII), the hydrocarbon resulting from the dehydration of ambrein, by condensing the Grignard derivative of the C_{17} bromide (XXXIX), derived from ambreinolide (XIX), with dihydro-γ-ionone (XXI).



(XXXVIII.)



(XXXIX.)

We know nothing about the biogenesis of ambrein; it is a fact that the sperm whale, having teeth, has different food habits from those of other whales. Its food consists mostly of cephalopods, and one of these, *Elledone moschata*, has a scent gland and is said to have a musk-like odour. Squalene could obviously be a precursor of ambrein. We have observed no change in squalene by treating it with dilute hydrochloric acid for a week, under conditions which could prevail in the stomach of the sperm whale.

Porphyrins. Okahara (*Jap. J. Med. Sci., II., Biochem.*, 1927, **1**, 247) has described a porphyrin isolated from ambergris and called ambraporphyrin. We have shown recently that ambraporphyrin is a mixture of protoporphyrin and *meso*porphyrin which are separable by chromatography (Lederer and Tixier, *Compt. rend.*, 1947, **224**, 531). It is known that proto-porphyrin is found in the intestine of vertebrates as a result of hæmorrhages in the intestine and that it is usually partly reduced to *meso*porphyrin by the intestinal bacteria (Zeile and Rau, *Z. physiol. Chem.*, 1937, **250**, 197; Grotepass and Defalque, *ibid.*, 1938, **252**, 155). We suppose that the numerous " beaks " of cephalopods, which are always found in ambergris, provoke hæmorrhages in the intestine of the sperm whale, with subsequent formation of proto- and *meso*-porphyrins. The lesions caused by the " beaks " of the cephalopods may well be the cause of the formation of ambergris.

Perfumers will be interested to learn that probably the greater part of the odorous products of ambergris are oxidation products of ambrein and that the long-lasting smell of ambergris may be partly explained by a constant autoxidation of ambrein with formation of volatile products. This oxidation is perhaps catalyzed by the appreciable amounts of copper contained in ambergris, which are derived from the hæmocyanin of the blood of the cephalopods in the food of the sperm whale.

* This paper definitely fixed the position of the angular methyl group of ambrein.

451. *Some Derivatives of Ethane-1 : 2-dithiol and 2-Mercaptoethyl Sulphoxides.*

By A. H. Ford-Moore.

The preparation of certain derivatives of phenyl vinyl sulphide, phenyl vinyl sulphoxide, and divinyl sulphoxide is described.

Iodosobenzene forms a useful reagent for the oxidation of sulphides to sulphoxides.

It was shown (Ford-Moore, Peters, and Wakelin, this vol., p. 1754) that the reaction $R'\cdot SO_2\cdot CH{:}CH_2 + SHR'' \longrightarrow R'\cdot SO_2\cdot CH_2\cdot CH_2\cdot SR''$ was reversible under conditions approaching the biological. It seemed of interest, therefore, to see whether corresponding sulphides and sulphoxides, $R'\cdot S\cdot CH_2\cdot CH_2\cdot SR''$ and $R'\cdot SO\cdot CH_2\cdot CH_2\cdot SR''$, would also respond to a similar type of fission. This paper describes the preparation of certain compounds of these two types.

(A) *Dithio-derivatives.*—Phenyl vinyl sulphide (I) is not nearly so reactive as the corresponding sulphone (*idem, ibid.*) and disulphides cannot as a rule be prepared by the direct addition of a thiol to it. In this case, phenyl 2-chloroethyl sulphide is used as the starting material and the desired substance is prepared by allowing it to react with the appropriate thiol in the presence of ethanolic potassium hydroxide.

(B) *Thionyl Sulphides.*—Two series of compounds in this group were examined, the first being derived from phenyl vinyl sulphoxide (II) and the second from divinyl sulphoxide (III).

$Ph\cdot S\cdot CH{:}CH_2$	$Ph\cdot SO\cdot CH{:}CH_2$	$SO(CH{:}CH_2)_2$
(I.)	(II.)	(III.)

When 2 : 2′-dichlorodiethyl sulphide (" mustard gas ") is oxidised with 30% hydrogen peroxide in acetic acid, excellent yields of the corresponding sulphoxide and sulphone can be obtained. The nature of the oxidation product depends on the proportion of peroxide to sulphide. Similar oxidations of phenyl 2-chloroethyl sulphide, phenyl 2-hydroxyethyl sulphide and phenyl 2-*p*-nitrobenzoyloxyethyl sulphide to their corresponding sulphones have been described (*idem, ibid.*). In the oxidation of the first of these, if the amount of peroxide corresponding to oxidation to the sulphoxide stage is taken, the product consists mainly of sulphone and unreacted sulphide. A very convenient reagent for converting sulphides into sulphoxides (when the hydrogen peroxide–acetic acid method fails) has been found in iodosobenzene, the reaction proceeding as follows: $PhIO + R'\cdot S\cdot R'' \longrightarrow PhI + R'\cdot SO\cdot R''$. Thiodiglycol (2 : 2′-dihydroxydiethyl sulphide) can be oxidised to 2 : 2′-dihydroxydiethyl sulphoxide by treatment with this reagent, though the oxidation can be carried out equally successfully with aqueous hydrogen peroxide. Iodosobenzene was therefore used to prepare (II) from phenyl 2-chloroethyl sulphide *via* phenyl 2-chloroethyl sulphoxide. The latter substance can be converted into (II) by warming it with aqueous potassium hydroxide. If ethanolic potassium hydroxide is used, a considerable amount of phenyl 2-ethoxyethyl sulphoxide is formed simultaneously.

Phenyl vinyl sulphoxide (II) lies between the sulphone and (I) in reactivity but more nearly approaches the former. It reacted with thiophenol in the presence of a trace of triethylamine with considerable evolution of heat but the product could not be induced to crystallise. It condensed with 2-mercaptobenzoic acid and with cysteine in the presence of aqueous sodium hydrogen carbonate or triethylamine to give the expected products.

The sulphoxide (III) resembles (II) in reactivity. Its preparation was described by Alexander and McCombie (*J.*, 1931, 1913) who obtained it by the action of triethylamine on 2 : 2′-di-iododiethyl sulphoxide, the corresponding 2 : 2′-dichloro-compound failing to react with this reagent. Levin (*J. pr. Chem.*, 1930, **127**, 77) also prepared it by the oxidation of divinyl sulphide (Bales and Nickelson, *J.*, 1922, **121**, 2137) with benzoyl hydroperoxide. A more convenient method, which does not involve the preparation of the di-iodo-compound, consists in boiling dichlorodiethyl sulphoxide with a slight excess of aqueous sodium carbonate and extracting the product with chloroform. It cannot be obtained by the oxidation of divinyl sulphide with hydrogen peroxide in acetic acid or acetone. It reacts with mercaptobenzoic acid and with cysteine to give the expected products.

Experimental.

2-Phenylthioethylthioacetic Acid, $Ph\cdot S\cdot CH_2\cdot CH_2\cdot S\cdot CH_2\cdot CO_2H$.—Thioglycollic acid (3·9 g.) was dissolved in 2N-ethanolic potassium hydroxide (42 c.c.), and phenyl 2-chloroethyl sulphide (6·4 g.) added.

After being heated under reflux for 1 hour on a steam-bath, the mixture was cooled and filtered, and most of the ethanol distilled from the filtrate. Water was added to the residue, and after the removal of a small amount of oily impurity, it was acidified with hydrochloric acid. The resulting *acid* was twice recrystallised from benzene–light petroleum (b. p. 40—60°) and then melted at 50—51° (Found : C, 52·7; H, 5·3. $C_{10}H_{12}O_2S_2$ requires C, 52·6; H, 5·3).

β-(2-Phenylthioethylthio)propionic Acid, Ph·S·CH_2·CH_2·S·CH_2·CH_2·CO_2H.—2-Phenylthioethanethiol, Ph·S·CH_2·CH_2·SH, was prepared by dissolving sodium (4·6 g.) in ethanol (200 c.c.), saturating the solution with hydrogen sulphide, adding a solution of phenyl 2-chloroethyl sulphide (34·5 g.) in ethanol (60 c.c.), and heating the mixture under reflux for 1 hour. The mixture was filtered hot, and the filtrate, on cooling, deposited crystals of di-(2-phenylthioethyl) sulphide, $S(CH_2·CH_2·SPh)_2$ (14 g.), m. p. 56—57° not altered on admixture with an authentic specimen from sodium thiophenoxide and 2 : 2′-dichlorodiethyl sulphide. The filtrate from these crystals was evaporated to dryness and extracted with 10% aqueous sodium hydroxide to remove a further small amount of trisulphide. The alkaline extract was acidified and extracted with chloroform, and the product isolated by distillation under reduced pressure after removal of the chloroform. The yield of material, b. p. 134°/11 mm., was 6·3 g.

A mixture of 2-chloropropionic acid (4·2 g.) and water (40 c.c.) was neutralised by addition of anhydrous sodium carbonate (2·1 g.), and a solution of 2-phenylthioethanethiol (6·2 g.) in 10% aqueous sodium hydroxide (15 c.c.) added. The mixture was heated to boiling, cooled, and acidified, giving 8·0 g. of crude *product*. This was crystallised first from benzene–light petroleum and then from carbon tetrachloride, and then melted at 78—79° (Found : C, 54·7; H, 5·7. $C_{11}H_{14}O_2S_2$ requires C, 54·5; H, 5·8%).

S-2-*Phenylthioethylcysteine*, Ph·S·CH_2·CH_2·S·CH_2·CH(NH_2)·CO_2H.—Cysteine hydrochloride (3·2 g.) and sodium hydrogen carbonate (1·8 g.) were dissolved in water (5 c.c.) and treated with a solution of phenyl 2-chloroethyl sulphide (3·5 g.) in ethanol (20 c.c.). The mixture was heated on a steam-bath, and 2N-ethanolic potassium hydroxide (10 c.c.) added dropwise during 0·5 hour. Heating was continued for a further 2 hours, at the end of which the mixture was cooled and filtered. The residue was dissolved in hot dilute hydrochloric acid, and the solution treated with sodium acetate till no longer acid to Congo-red. The *product* was filtered off, washed with cold distilled water, and dried *in vacuo*; m. p. 208° (decomp.) (Found : C, 51, 45; H, 6·2; N, 5·4. $C_{11}H_{15}O_2NS_2$ requires C, 51·5; H, 5·9; N, 5·4%).

Divinyl Sulphoxide (III).—2 : 2′-Dichlorodiethyl sulphoxide (100 g.), hydrated sodium carbonate (172 g.), and water (200 c.c.) were heated to boiling in a 700-c.c. flask fitted with an efficient reflux condenser. When a vigorous reaction set in, the source of heat was withdrawn till it had moderated, and heat was again applied for a further hour. After cooling, the mixture was made just acid to Congo-red by the cautious addition of hydrochloric acid (*d* 1·18) and extracted with three 100-c.c. portions of chloroform. The extracts were separated and dried ($MgSO_4$), and the solvent removed. The residue was fractionated under reduced pressure and collected at 72—74°/8 mm. (Alexander and McCombie, *loc. cit.*, give b. p. 86—87°/18 mm.; Levin, *loc. cit.*, gives b. p. 58—59°/3·5 mm., 67—68°/5—6 mm.); yield, 44—47 g. (76—81%).

Di-[2-(2′-*amino*-2′-*carboxyethylthio*)*ethyl*] *Sulphoxide*, SO[CH_2·CH_2·S·CH_2·CH(NH_2)·CO_2H]$_2$.—Sodium hydrogen carbonate (7·5 g.), dissolved in water (70 c.c.), was saturated with carbon dioxide, and cysteine (7·1 g.) and divinyl sulphoxide (2·8 g.) were added. The mixture was warmed to 50° for 10 minutes and kept at room temperature overnight. It was made just acid to litmus by cautious addition of 25% acetic acid, and evaporated to dryness under reduced pressure, the residue being extracted twice with hot ethanol to remove sodium acetate. The residue after this extraction was dissolved in a little boiling water containing a few drops of acetic acid (charcoal) and filtered, and ethanol was added to the hot filtrate to turbidity. The product that separated on cooling was filtered off and suspended in boiling ethanol, and water added dropwise till dissolution just took place. The pure *compound* separated on cooling; m. p. 226—227° (decomp.) (Found : C, 34·7; H, 5·8; N, 8·0; S, 27·7. $C_{10}H_{20}O_6N_2S_4$ requires C, 34·9; H, 5·85; N, 8·1; S, 27·9).

2 : 2′-*Di-*(*o-carboxyphenylthio*)*diethyl Sulphoxide*, SO(CH_2·CH_2·S·C_6H_4·CO_2H)$_2$.—*o*-Mercaptobenzoic acid (7·5 g.), sodium hydrogen carbonate (7·5 g.), divinyl sulphoxide (2·0 g.), and water (60 c.c.) were warmed on a water-bath for 10 minutes. After 1 hour at room temperature, the mixture was acidified with hydrochloric acid. The product separated in a sticky condition but rapidly crystallised when washed with cold water. It was sparingly soluble in hot ethanol, methyl ethyl ketone, ethyl acetate, or benzene, and was crystallised from acetic acid; m. p. 202° (decomp.) (Found : C, 52·4; H, 4·4. $C_{18}H_{18}O_5S_3$ requires C, 52·7; H, 4·4%).

2 : 2′-*Dihydroxydiethyl Sulphoxide*.—Thiodiglycol (12 g.) in water (50 c.c.) was heated on a steam-bath, and iodosobenzene (25 g.) added. The reaction appeared to be complete in about 15 minutes. The mixture was cooled and filtered, and the residue washed with water (10 c.c.). The iodobenzene in the filtrate (13 g.) was separated from the aqueous portion, and the latter taken to dryness *in vacuo* on a steam-bath. The residue when cold was treated with acetone and filtered, giving 13 g. of crude product. This was crystallised from ethanol, from which 11 g. of pure sulphoxide separated in large needles, m. p. 111° (Levin, *loc. cit.*, gives 111—112°), unaltered on admixture with a specimen prepared from thiodiglycol by oxidation with aqueous hydrogen peroxide.

Phenyl Vinyl Sulphoxide (II).—Iodosobenzene (13 g.), dried *in vacuo* over sulphuric acid, phenyl 2-chloroethyl sulphide, and benzene (40 c.c.) were heated under reflux on a steam-bath till all the iodosobenzene had disappeared (9·5 hours). The mixture was filtered from a little solid impurity, and the benzene distilled from the filtrate. The iodobenzene formed in the reaction was next removed under reduced pressure below 100°, leaving a residue of crude phenyl 2-chloroethyl sulphoxide that could not be made to solidify and decomposed on attempted distillation under reduced pressure.

This was heated under reflux for 1·5 hours with a solution of potassium hydroxide (3 g.) in water (30 c.c.) and cooled, and the product extracted with chloroform. After removal of solvent, the residue was distilled under reduced pressure and collected at 98—105°/0·5 mm. On redistillation, it boiled at 93—95°/0·2 mm.; yield 4·8 g. (53%, based on the phenyl 2-chloroethyl sulphide) (Found : C, 62·8; H, 5·3. C_8H_8OS requires C, 63·15; H, 5·3%).

When ethanolic potassium hydroxide was used in place of the aqueous solution, a considerable

amount of somewhat impure *phenyl 2-ethoxyethyl sulphoxide*, b. p. 128—136°/0·3 mm., was formed (Found : C, 60·15; H, 7·8. $C_{10}H_{14}O_2S$ requires C, 60·6; H, 7·1%).

Phenyl 2-(o-Carboxyphenylthio)ethyl Sulphoxide, $Ph{\cdot}SO{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}C_6H_4{\cdot}CO_2H$.—*o*-Mercaptobenzoic acid (1·5 g.) was dissolved in water (20 c.c.) containing sodium hydrogen carbonate (2·0 g.). Phenyl vinyl sulphoxide (1·5 g.) was added, and the mixture warmed on a steam-bath with occasional shaking. The sulphoxide dissolved in about 0·5 hour. After a further 0·5 hour's heating, the mixture was cooled and acidified. The water was decanted from the sticky precipitate, which rapidly crystallised on treatment with hot benzene. It was sparingly soluble in hot benzene, readily so in cold methanol, and was recrystallised from ethyl acetate containing a little methanol; m. p. 154° (Found : C, 58·3; H, 4·7. $C_{15}H_{14}O_3S_2$ requires C, 58·8; H, 4·6%).

S-2-*Phenylsulphinylethylcysteine*, $Ph{\cdot}SO{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH(NH_2){\cdot}CO_2H$.—Phenyl vinyl sulphoxide (3·0 g.) was added to a mixture of cysteine (2·4 g.), water (30 c.c.), and triethylamine (0·1 g.). The reaction started in the cold, the temperature rising about 10° and the sulphoxide dissolving in *ca.* 15 minutes. After being kept overnight, the water was removed under reduced pressure and the residue treated with ethanol. After being filtered off, the *product* was recrystallised by boiling with ethanol and adding water dropwise till dissolution just took place. It was then obtained pure and decomposed without melting at 181—182° (Found : C, 47·95; H, 5·45; N, 5·3; S, 23·3. $C_{11}H_{15}O_3NS_2$ requires C, 48·3; H, 5·5; N, 5·1; S, 23·5%).

2-*Phenylsulphinylethylthioacetic Acid*, $Ph{\cdot}SO{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H$.—Phenyl vinyl sulphoxide and thioglycollic acid readily combine in the presence of aqueous sodium hydrogen carbonate but the free acid on liberation tends to dissociate rather rapidly into the starting materials. It can be isolated as its *barium* salt as follows. The sulphoxide (1·8 g.), thioglycollic acid (1·1 g.), and saturated aqueous baryta (32 c.c.) were kept at room temperature for 1 hour. The mixture was then saturated with carbon dioxide and filtered, and the filtrate concentrated under reduced pressure. When kept for several days *in vacuo* over sulphuric acid, the salt crystallised (Found : C, 39·05; H, 3·7; S, 20·3; Ba, 22·8. $C_{20}H_{22}O_6S_4Ba$ requires C, 39·5; H, 3·6; S, 20·55; Ba, 22·2%).

The microanalyses were carried out by Messrs. Weiler and Strauss and by Mr. G. Ingram.

This work, part of which was carried out while the author was a member of Sir Robert Robinson's team at the Dyson Perrins Laboratory, Oxford, is published by permission of the Chief Scientist, Ministry of Supply.

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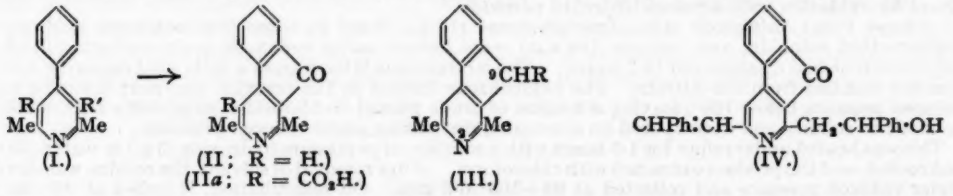
452. *Some Derivatives of* 1 : 3-*Dimethyl-2-azafluorenone.*

By H. J. KAHN, V. PETROW, E. L. REWALD, and B. STURGEON.

Methods for the ready synthesis of 1 : 3-dimethyl-2-azafluorenone (II) and certain of its functional derivatives, required for biological study, have been developed. The chemistry of the group has been extended and compounds such as 9-*amino*-1 : 3-*dimethyl-2-azafluorenone* (III; R = NH_2) have been prepared.

1 : 3-DIMETHYL-2-AZAFLUORENONE (II), required for collateral studies (Petrow, *J.*, 1946, 200, 888), was kindly examined at our request by Dr. R. H. Thorp (Wellcome Physiological Research Laboratories, on behalf of The Therapeutic Research Corporation of Great Britain Ltd.) and found to be a better spasmolytic agent than papaverine. We therefore prepared further compounds of this group for biological study, the results of which will be reported elsewhere.

Mills, Palmer, and Tomkinson (*J.*, 1924, 2365) prepared 1 : 3-dimethyl-2-azafluorenone (II) by decarboxylation of its 4-carboxylic acid (II*a*) in 500-mg. quantities. Borsche and Hahn (*Annalen*, 1939, **537**, 219), on the other hand, employed a Friedel–Crafts ring closure on 4-phenyllutidine-3-carboxyl chloride (I; R′ = COCl, R = H), preparing the required acid by an unwieldy process involving regeneration from its copper salt with hydrogen sulphide. These methods proved unsatisfactory for the preparation of 1 : 3-dimethyl-2-azafluorenone (II) in quantity, the compound being ultimately prepared as follows. Method (i) : 1 : 3-dimethyl-2-azafluorenone-4-carboxylic acid (II*a*) was prepared essentially as described by Mills *et al.*



(I.) (II; R = H.) (IIa; R = CO_2H.) (III.) (IV.)

(*loc. cit.*) but was decarboxylated by heating in a neutral solvent such as liquid paraffin; large quantities of (II) were thus readily obtained for the first time. Method (ii) : ethyl 4-phenyl-

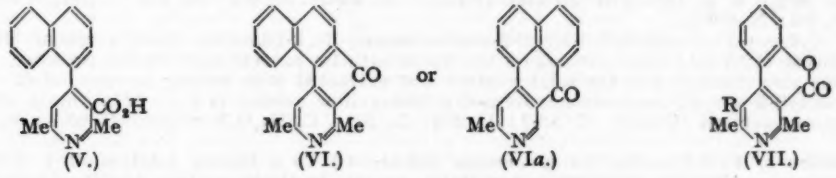
lutidine-3 : 5-dicarboxylate (I; R = R′ = CO_2Et) was converted into the acid ester (I; R′ = CO_2Et, R = CO_2H) by partial hydrolysis (cf. Hantzsch, *Ber.*, 1884, **17**, 2910), thence into ethyl 4-phenyl-lutidine-3-carboxylate (I; R′ = CO_2Et, R = H) by decarboxylation, and into the corresponding potassium salt by hydrolysis (see Experimental). Treatment of this salt with dilute sulphuric acid gave *4-phenyl-lutidine-3-carboxylic acid sulphate*, from which (II) was obtained in *ca.* 90% yield by ring closure with sulphuric acid or in somewhat lower yield by the Friedel–Crafts route.

Reduction of (II) with zinc dust in aqueous alcoholic ammonia gave 1 : 3-*dimethyl-2-azafluorenol* (III; R = OH), characterised as the *picrate*. Further reduction with sodium in alcohol led, rather surprisingly, to the loss of the 9-hydroxyl group and the formation of 1 : 3-*dimethyl-2-azahexahydrofluorene* together with some 1 : 3-dimethyl-2-azafluorene. Condensation of (II) with benzaldehyde in the presence of zinc chloride gave 1-(*2′-hydroxy-2′-phenylethyl*)-3-*styryl-2-azafluorenone* (IV), but this compound proved too insoluble for biological study. Further experiments in this direction were therefore discontinued.

Reduction of 1 : 3-dimethyl-2-azafluorenone oxime with zinc dust and acetic acid gave 9-*acetamido*-1 : 3-*dimethyl-2-azafluorene* (III; R = NHAc) (20%) together with appreciable quantities of 1 : 3-dimethyl-2-azafluorene (20%). Reduction with zinc dust and acetic anhydride, however, was more satisfactory (III; R = NHAc) being obtained in nearly quantitative yield. 9-Acetamido-1 : 3-dimethyl-2-azafluorene proved remarkably resistant to hydrolysis, being recovered unchanged after prolonged heating with concentrated hydrochloric acid or with 30% sulphuric acid (see Bennett, Jewsbury, and Dupuis, *J. Amer. Chem. Soc.*, 1946, **68**, 2489). However, syrupy phosphoric acid at 200° gave smoothly 9-*amino*-1 : 3-*dimethyl-2-azafluorene* (III; R = NH_2), a strong base which rapidly absorbed carbon dioxide on exposure to air. Its structure followed from conversion into the *benzylidene-* and the *benzoyl* derivative. Nitration of (III; R = NHAc) gave a *nitro*-derivative in very high yield, to which the constitution 7-*nitro*-9-*acetamido*-1 : 3-*dimethyl-2-azafluorene* has been provisionally assigned (cf. Bennett *et al.*, *loc. cit.*); reduction with zinc dust and acetic anhydride gave 7(?) : 9-*diacetamido*-1 : 3-*dimethyl-2-azafluorene*, which could not be hydrolysed.

Some derivatives of (II) were prepared by method (ii) (above).

1-Naphthaldehyde gave 4-1′-*naphthyl-lutidine-3-carboxylic acid* (V), the acid chloride of which passed smoothly into a homogeneous *product*, $C_{18}H_{13}ON$, to which the constitution



1 : 3-*dimethyl-2-aza-5* : 6-*benzfluorenone* (VI) has been assigned. Its alternative formulation as an azabenzanthrone (VI*a*) seems unlikely, as ring closure of aryl analogues of (V) which are substituted by a negative grouping in the position occupied by the ring nitrogen of (V) give benzfluorenones exclusively on cyclisation (Baddar and Gindy, *J.*, 1944, 450).

4-o-*Methoxyphenyl-lutidine-3-carboxylic acid sulphate*, prepared from *o*-anisaldehyde, gave 10-*keto*-1 : 3-*dimethyl-9-oxa-2-aza*-9 : 10-*dihydrophenanthrene* (VII; R = H) on ring-closure of the acid chloride. The constitution assigned to this compound followed from its synthesis through 4-*o*-hydroxyphenyl-lutidine-3 : 5-dicarboxylic acid. 4-m-*Methoxyphenyl-lutidine-3-carboxylic acid* and 4-p-*methoxyphenyl-lutidine-3-carboxylic acid sulphate* behaved normally giving 8(6)-*methoxy-* and 7-*methoxy*-1 : 3-*dimethyl-2-azafluorenone*, respectively, which were converted into the corresponding *hydroxy*-derivatives by hydrobromic acid. Attempts to prepare 8(6)-hydroxy-1 : 3-dimethyl-2-azafluorenone directly from *m*-hydroxybenzaldehyde were unsuccessful (see Experimental).

m- and *p*-Nitrobenzaldehyde gave 4-m- and 4-p-*nitrophenyl-lutidine-3-carboxylic acid*, but all attempts at the ring closure of these compounds proved unsuccessful. 4-*p*-Benzamidophenyl-lutidine-3-carboxylic acid, isolated as the *acetate*, likewise failed to give an azafluorenone under a variety of experimental conditions. Attempts to prove the structure of the nitro-derivative of (II) described in an earlier publication (Petrow, *J.*, 1946, 888) were thus unsuccessful.

Abandonment of the work in August 1948 left certain syntheses half completed. These are recorded in the Experimental section.

Experimental.

M.p.s are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

1 : 3-*Dimethyl*-2-*azafluorenone*.—(i) Finely powdered 1 : 3-dimethyl-2-azafluorenone-5-carboxylic acid (Mills, Palmer, and Tomkinson, *loc. cit.*) was rapidly added to 10 parts of well-stirred liquid paraffin maintained at 300—320°. Decarboxylation was complete in *ca.* 20 minutes. After being set aside overnight at room temperature the crystalline product was collected, washed with small quantities of ice-cold light petroleum, and recrystallised from ethanol, giving 1 : 3-dimethyl-2-azafluorenone, m. p. 159—160°, not depressed in admixture with an authentic specimen.

(ii) Ethyl 4-phenyl-lutidine-3-carboxylate (10 g.; Petrow, *loc. cit.*), potassium hydroxide (7·5 g.), and ethanol (25 ml.) were heated under reflux on the water-bath for 4 hours. After being kept at 0° for 24 hours the potassium salt was collected and dissolved in a small amount of water, and the solution made acid to Congo-red with concentrated sulphuric acid. The precipitate was collected and recrystallised from 2N-sulphuric acid. *4-Phenyl-lutidine-3-carboxylic acid sulphate* formed felted needles, m. p. 256—257° (decomp.) (7·8 g., 73%) (Found: S, 6·3. $C_{14}H_{13}O_2N,\frac{1}{2}H_2SO_4$ requires S, 5·8%).

The sulphate (10 g.) and concentrated sulphuric acid (40 ml.) were heated on the water-bath for 2 hours, whereafter the solution was poured into water and made alkaline with sodium hydroxide. The precipitate was collected and recrystallised from alcohol, yielding glistening needles of 1 : 3-dimethyl-2-azafluorenone, m. p. 159—160° (Found: C, 80·3; H, 5·2. Calc. for $C_{14}H_{11}ON$: C, 80·4; H, 5·3%), in nearly quantitative yield. The compound gave no depression in m. p. on admixture with an authentic specimen (Mills *et al.*, *loc. cit.*).

The *isethionate* separated in colourless prisms, m. p. 162·5—163° (Found: S, 9·7. $C_{14}H_{11}ON,C_2H_6O_4S$ requires S, 9·5%), from ice-cold methanol.

1 : 3-*Dimethyl*-2-*azafluoren*-9-*ol*.—1 : 3-Dimethyl-2-azafluorenone (20 g.), aqueous ammonia (500 ml.; *d* 0·88), zinc dust (150 g.), and alcohol (100 ml.) were heated under reflux for 2—3 hours. The hot mixture was filtered, the residues were washed with boiling alcohol, and the bulked filtrates were concentrated until crystallisation commenced. 1 : 3-*Dimethyl*-2-*azafluoren*-9-*ol* was collected and recrystallised from benzene; m. p. 172—173° (Found: C, 74·9; H, 6·0. $C_{14}H_{13}ON$ requires C, 74·6; H, 6·2%); yield, 14 g. (70%). The *picrate* formed yellow needles, m. p. 248—249° (Found: N, 12·7. $C_{14}H_{13}ON,C_6H_3O_7N_3$ requires N, 13·0%), from alcohol.

1 : 3-*Dimethyl*-2-*azahexahydrofluorene*.—1 : 3-Dimethyl-2-azafluorenol (20 g.) in ethanol (450 ml.) was treated with sodium (60 g.) during 1 hour under reflux. Water (500 ml.) was added and the alcohol removed on the water-bath. The oil was extracted with chloroform, and the evaporated extract taken up in alcohol and treated with picric acid (20 g.). The product which separated was identified as 1 : 3-*dimethyl*-2-*azafluorene picrate*, yellow needles from alcohol, m. p. 250° (decomp.) (Found: N, 13·1. $C_{14}H_{13}N,C_6H_3O_7N_3$ requires N, 13·2%), not depressed on admixture with an authentic specimen (see below). The picrate mother-liquors, made alkaline with sodium hydroxide solution and extracted with chloroform, gave 1 : 3-*dimethyl*-2-*azahexahydrofluorene* as a pale yellow oil (5 g., 25%), b. p. 155—160°/20 mm. (Found: C, 83·5; H, 9·4; N, 6·4. $C_{14}H_{19}N$ requires C, 83·7; H, 9·4; N, 6·9%).

1-(2′-*Hydroxy*-2′-*phenylethyl*)-3-*styryl*-2-*azafluorenone*.—1 : 3-Dimethyl-2-azafluorenone (10 g.) and benzaldehyde (12·5 ml.) were warmed on the water-bath for several hours in the presence of a little anhydrous zinc chloride, and the solid product was extracted with boiling acetone. 1-(2′-*Hydroxy*-2′-*phenylethyl*)-3-*styryl*-2-*azafluorenone* formed golden-yellow needles (4·2 g., 22%), m. p. 169—170°, from aqueous acetone (Found: C, 83·7; H, 5·0; N, 3·7. $C_{28}H_{21}O_2N$ requires C, 83·4; H, 5·2; N, 3·5%).

Reduction of 1 : 3-*Dimethyl*-2-*azafluorenone Oxime*.—(i) To a boiling solution of 1 : 3-dimethyl-2-azafluorenone oxime (10 g.) (Borsche and Hahn, *loc. cit.*) in glacial acetic acid (70 ml.) under reflux was added in portions zinc dust (18 g.), heating being continued for a further hour. The mixture was added to water (200 ml.), and the filtered solution treated with excess of aqueous ammonia. The precipitated solids were collected, dried, and extracted with benzene–methanol. The more sparingly soluble fraction (m. p. 260—270°) was recrystallised from alcohol, giving needles of 9-*acetamido*-1 : 3-*dimethyl*-2-*azafluorene*, m. p. 274—275° (Found: C, 76·4; H, 6·3; N, 11·2. $C_{16}H_{16}ON_2$ requires C, 76·5; H, 6·3; N, 11·1%). The benzene–methanol mother-liquors were saturated with hydrogen chloride, yielding 1 : 3-dimethyl-2-azafluorene hydrochloride, m. p. 300° after crystallisation from ethanol (Found: Cl, 15·1. Calc. for $C_{14}H_{13}N,HCl$: Cl, 15·3%). The free base formed needles (from light petroleum), m. p. 97—98° (Found: N, 7·4. Calc. for $C_{14}H_{13}N$: N, 7·2%), not depressed on admixture with an authentic specimen. The *picrate* formed yellow needles, m. p. 250° (decomp.) (Found: N, 13·6. $C_{14}H_{13}N,C_6H_3O_7N_3$ requires N, 13·2%), from alcohol.

(ii) A warm solution of 1 : 3-dimethyl-2-azafluorenone oxime (4·5 g.; Borsche and Hahn, *loc. cit.*) and anhydrous sodium acetate (4·5 g.) in acetic anhydride (45 g.) was treated with zinc dust (9 g.) added in portions, the reaction being allowed to moderate after each addition. The mixture was finally heated under reflux for 1 hour and then filtered hot, and the filtrate poured into ice–water (200 ml.). The solution was made alkaline with aqueous sodium hydroxide, and the bulky precipitate collected and recrystallised from aqueous alcohol. 9-Acetamido-1 : 3-dimethyl-2-azafluorene separated in long needles, m. p. 274—275° (3·6 g., 74%) (Found: C, 76·4; H, 6·5; N, 11·2. Calc. for $C_{16}H_{16}ON_2$: C, 76·5; H, 6·3; N, 11·1%).

9-*Amino*-1 : 3-*dimethyl*-2-*azafluorene*.—9-Acetamido-1 : 3-dimethyl-2-azafluorene (15 g.) was dissolved in syrupy phosphoric acid (75 ml.) and heated in an oil-bath at 180—200° for 1 hour. The cooled solution was diluted with water and made alkaline with aqueous ammonia. The oily precipitate, which solidified when kept, was collected, washed with water, and dried *in vacuo* over phosphoric oxide. The dried material was extracted with benzene, and the benzene extract recrystallised from light petroleum at room temperature under reduced pressure. 9-*Amino*-1 : 3-*dimethyl*-2-*azafluorene* formed long white needles (11·7 g., 94%), m. p. 89°, which absorbed carbon dioxide on

exposure to the air (Found : C, 80·0; H, 6·7; N, 13·4. $C_{14}H_{16}N_2$ requires C, 80·0; H, 6·7; N, 13·4%). The *dihydrochloride* formed white platelets, m. p. 260° (decomp.) (Found : Cl, 24·0. $C_{14}H_{16}N_2,2HCl$ requires Cl, 25·0%), from alcohol. The *monobenzoyl* derivative formed feathery white needles, m. p. 283° (Found : C, 80·2; H, 5·8; N, 9·2. $C_{21}H_{18}ON_2$ requires C, 80·3; H, 5·7; N, 8·9%), from alcohol. The *benzylidene* derivative formed platelets, m. p. 188° (Found : C, 84·4; H, 6·0; N, 9·7. $C_{21}H_{18}N_2$ requires C, 84·6; H, 6·0; N, 9·4%), from aqueous alcohol.

7(?)-*Nitro*-9-*acetamido*-1 : 3-*dimethyl*-2-*azafluorene*.—9-Acetamido-1 : 3-dimethyl-2-azafluorene (5 g.) dissolved in concentrated sulphuric acid (20 ml.) was treated with finely powdered potassium nitrate (2 g.) during 3 hours, the mixture being stirred mechanically at room temperature. The mixture was poured on crushed ice and made alkaline with aqueous ammonia. The precipitate was collected and extracted with a little boiling alcohol. The residue, on crystallisation from a large volume of alcohol, gave felted needles of 7-*nitro*-9-*acetamido*-1 : 3-*dimethyl*-2-*azafluorene*, m. p. 300° (decomp.) (Found : C, 64·5; H, 5·2; N, 13·6. $C_{16}H_{15}O_3N_3$ requires C, 64·8; H, 5·1; N, 14·1%), in nearly quantitative yield.

7(?) : 9-*Diacetamido*-1 : 3-*dimethyl*-2-*azafluorene*.—7(?)-Nitro-9-acetamido-1 : 3-dimethyl-2-azafluorene (2 g.), suspended in boiling acetic anhydride (80 ml.), was treated with zinc dust (4 g.) added in portions. The mixture was filtered hot and the solids were washed with acetic anhydride. The combined filtrates were decomposed with water and made alkaline with sodium hydroxide solution. The precipitated solids were collected and purified from aqueous alcohol, giving 7 : 9-*diacetamido*-1 : 3-*dimethyl*-2-*azafluorene*, ivory-coloured needles, m. p. >300° (Found : C, 69·8; H, 6·4; N, 13·6. $C_{18}H_{19}O_2N_3$ requires C, 69·9; H, 6·2; N, 13·6%).

Ethyl 4-1′-*Naphthyldihydrolutidine*-3 : 5-*dicarboxylate*.—1-Naphthaldehyde (13 g.), ethyl 2-aminocrotonate (11 g.), and ethyl acetoacetate (11 g.) were heated on the water-bath for 8 hours. The semi-solid mixture was triturated with hot methanol, and the crystalline residue heated under reflux with acetic anhydride (10 volumes). The solution was poured into water and made alkaline with aqueous ammonia, the precipitate being collected and recrystallised from aqueous alcohol. *Ethyl* 4-1′-*naphthyldihydrolutidine*-3 : 5-*dicarboxylate* formed cream-coloured plates, m. p. 197·5—198° (Found : C, 72·8; H, 6·8; N, 3·5. $C_{23}H_{25}O_4N$ requires C, 72·8; H, 6·6; N, 3·7%).

Ethyl 4-1′-*Naphthyl-lutidine*-3 : 5-*dicarboxylate*.—The foregoing dihydro-ester (2·5 g.) in glacial acetic acid (20 ml.) was treated at 100° with chromium trioxide (500 mg.) dissolved in a little water. After being heated for 10 minutes on the water-bath the mixture was made alkaline with aqueous ammonia, and the product extracted with chloroform and recrystallised from light petroleum (b. p. 40—60°). *Ethyl* 4-1′-*naphthyl-lutidine*-3 : 5-*dicarboxylate* formed rhombic crystals (2·1 g., 85%), m. p. 58°, b. p. 272°/20 mm. (Found : C, 73·0; H, 6·1. $C_{23}H_{23}O_4N$ requires C, 73·2; H, 6·1%).

3-*Carbethoxy*-4-1′-*naphthyl-lutidine*-5-*carboxylic Acid*.—The foregoing ester (87·5 g.) and potassium hydroxide (14 g.) were heated under reflux in ethanol (140 ml.) for 100 hours, whereafter the alcohol was removed on the water-bath, and the residual liquid diluted with water. Unchanged material separated and was removed. The filtrate was then neutralised with dilute sulphuric acid, and the precipitate collected and recrystallised from alcohol. 3-*Carbethoxy*-4-1′-*naphthyl-lutidine*-5-*carboxylic acid* formed colourless platelets (46 g., 70%), m. p. 238—239° (Found : C, 72·7; H, 5·5; N, 4·5. $C_{21}H_{19}O_4N$ requires C, 72·2; H, 5·4; N, 4·0%), from ethanol–light petroleum.

Ethyl 4-1′-*Naphthyl-lutidine*-3-*carboxylate*.—The foregoing acid ester (20 g.) was heated at 260—270° in a metal-bath for 30 minutes, and the residue distilled under reduced pressure. *Ethyl* 4-1′-*naphthyl-lutidine*-3-*carboxylate* formed a pale yellow viscous oil (14·5 g., 85%), b. p. 264—266°/20 mm. (Found : C, 78·4; H, 6·4; N, 4·9. $C_{20}H_{19}O_2N$ requires C, 78·7; H, 6·2; N, 4·6%).

4-1′-*Naphthyl-lutidine*-3-*carboxylic Acid*.—Ethyl 4-1′-naphthyl-lutidine-3-carboxylate (37·1 g.), potassium hydroxide (8 g.), and alcohol (80 ml.) were heated under reflux for 45 hours. Alcohol was removed on the water-bath, the residue dissolved in water and extracted with ether to remove unchanged material, and the aqueous solution treated with sulphuric acid (3·8 ml.). The precipitate was collected and recrystallised from alcohol–light petroleum. 4-1′-*Naphthyl-lutidine*-3-*carboxylic acid* formed colourless prismatic needles, m. p. 265° (Found : C, 77·9; H, 5·5; N, 5·1. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·4; N, 5·1%). Yield, 22·6 g. (68%).

1 : 3-*Dimethyl*-2-*aza*-5 : 6-*benzfluorenone*.—The foregoing acid (2 g.) was treated with thionyl chloride (20 ml.) under reflux for 30 minutes. The excess of thionyl chloride was removed under reduced pressure, and the residue taken up in nitrobenzene (20 ml.). The mixture was treated with aluminium chloride (4 g.) and kept at 60° for 3 hours. The nitrobenzene was removed in steam, and the aqueous solution saturated with sodium acetate. The precipitate was collected and recrystallised from aqueous alcohol containing a pellet of potassium hydroxide. 1 : 3-*Dimethyl*-2-*aza*-5 : 6-*benzfluorenone* separated from benzene–ligroin in very small golden needles (1·1 g., 59%), m. p. 212—213·5° (Found : C, 83·4; H, 5·0; N, 5·4. $C_{18}H_{13}ON$ requires C, 83·4; H, 5·0; N, 5·4%). The *isethionate* formed mustard-coloured prisms, m. p. 234·5—235·5° (Found : S, 8·4. $C_{18}H_{13}ON,C_2H_6O_4S$ requires S, 8·3%), from alcohol–acetone.

4-*o*-*Methoxyphenyl-lutidine*-3 : 5-*dicarboxylic Acid*.—Ethyl 4-*o*-methoxyphenyl-lutidine-3 : 5-dicarboxylate (85 g.; Hinkel and Madel, *J.*, 1929, 752), potassium hydroxide (130 g.), and ethanol (450 ml.) were heated under reflux on the water-bath for 4 hours. After being kept at 0° for 24 hours the potassium salt was collected and dissolved in water (250 ml.), and the solution made acid to Congo-red with dilute sulphuric acid. The precipitate was collected and repeatedly crystallised from glacial acetic acid. 4-*o*-Methoxyphenyl-lutidine-3 : 5-dicarboxylic acid formed fine white crystals, m. p. 314° (decomp.), which could not be obtained analytically pure (Found : C, 61·8; H, 5·0; N, 4·5. Calc. for $C_{16}H_{15}O_5N$: C, 63·8; H, 5·0; N, 4·7%). Yield, 53 g. (74%).

10-*Keto*-1 : 3-*dimethyl*-9-*oxa*-2-*aza*-9 : 10-*dihydrophenanthrene*-4-*carboxylic Acid*.—The foregoing acid (10 g.) was heated under reflux for 1 hour with hydrobromic acid (100 ml.; constant-boiling). The thin yellow crystals of the resulting hydrobromide were collected, suspended in water (150 ml.), and made alkaline with potassium hydroxide (4·0 g.). The mixture was filtered, the filtrate made acid

to Congo-red with dilute sulphuric acid, and the precipitate collected and recrystallised from aqueous alcohol. 10-*Keto*-1 : 3-*dimethyl*-9-*oxa*-2-*aza*-9 : 10-*dihydrophenanthrene*-4-*carboxylic acid* formed white needles, m. p. 257·5° (decomp.) (Found : C, 66·9; H, 3·7; N, 5·3. $C_{15}H_{11}O_4N$ requires C, 66·9; H, 4·1; N, 5·3%).

Unless otherwise stated the procedure described in detail for the 1-naphthyl series was employed in the preparation of the compounds listed below.

5-*Carbethoxy*-4-o-*methoxyphenyl-lutidine*-3-*carboxylic acid*, white crystals from dilute alcohol, m. p. 195—196° (Found : C, 65·7; H, 5·8; N, 4·6. $C_{18}H_{19}O_5N$ requires C, 65·6; H, 5·8; N, 4·3%); yield, 60%.

Ethyl 4-o-*methoxyphenyl-lutidine*-3-*carboxylate*, a faintly yellow viscous oil, b. p. 238°/30 mm. (Found : N, 5·4. $C_{17}H_{19}O_3N$ requires N, 4·9%); yield, 75%.

4-*o*-Methoxyphenyl-lutidine-3-carboxylic acid *sulphate*, white crystals (from alcohol–light petroleum), m. p. 170° (Found : S, 5·0. $C_{15}H_{15}O_3N,\frac{1}{2}H_2SO_4$ requires S, 5·2%); yield, 56%.

10-*Keto*-1 : 3-*dimethyl*-9-*oxa*-2-*aza*-9 : 10-*dihydrophenanthrene*.—(i) 10-Keto-1 : 3-dimethyl-9-*oxa*-2-*aza*-9 : 10-dihydrophenanthrene-5-carboxylic acid (10 g.) was heated above its m. p. for 5 minutes, and the residue crystallised from dilute acetic acid. 10-*Keto*-1 : 3-*dimethyl*-9-*oxa*-2-*aza*-9 : 10-*dihydrophenanthrene* formed squat angular rods (5·9 g., 70%), m. p. 203—204° (Found : C, 74·5; H, 5·0; N, 6·3. $C_{14}H_{11}O_3N$ requires C, 74·7; H, 4·9; N, 6·2%).

(ii) 4-*o*-Methoxyphenyl-lutidine-3-carboxylic acid sulphate (10 g.) and thionyl chloride (50 ml.) were heated under reflux for 10 minutes. Excess of thionyl chloride was removed under reduced pressure, and the residue dissolved in nitrobenzene (80 ml.). The solution was treated with aluminium chloride (9 g.) and warmed for 2 hours at 50°. The nitrobenzene was removed in steam, and the aqueous residues saturated with sodium acetate. The precipitate was collected and recrystallised from aqueous alcohol, giving 10-*keto*-1 : 3-*dimethyl*-9-*oxa*-2-*aza*-9 : 10-*dihydrophenanthrene*, white crystals, m. p. 203—204° (Found : C, 74·3; H, 5·0; N, 6·4. Calc. for $C_{14}H_{11}O_3N$: C, 74·7; H, 4·9; N, 6·2%). The compound gave no depression of melting point on admixture with a specimen prepared by method (i).

Ethyl 4-m-*Acetoxyphenyldihydrolutidine*-3 : 5-*dicarboxylate*.—Ethyl 4-*m*-hydroxyphenyldihydrolutidine-3 : 5-dicarboxylate (100 g.) (Hinkel and Madel, *loc. cit.*) was heated under reflux with acetic anhydride (250 ml.) for 30 minutes, and the cooled mixture decomposed with water. The oily precipitate solidified when kept and was recrystallised from aqueous alcohol. *Ethyl* 4-m-*acetoxyphenyl-dihydrolutidine*-3 : 5-*dicarboxylate* (105 g., 96%) had m. p. 125—126° (Found : C, 64·6; H, 6·5; $C_{21}H_{25}O_6N$ requires C, 65·1; H, 6·5%).

Ethyl 4-m-*Acetoxyphenyl-lutidine*-3 : 5-*dicarboxylate*.—The foregoing ester (10·5 g.) in glacial acetic acid (25 ml.) was treated with chromium trioxide (2·1 g.) in water (5 ml.) and glacial acetic acid (5 ml.). The mixture was warmed on the water-bath for 10 minutes and made alkaline with aqueous ammonia. The oily precipitate was recrystallised from aqueous methanol, giving *ethyl* 4-m-*acetoxyphenyl-lutidine*-3 : 5-*dicarboxylate*, m. p. 98° (Found : C, 65·4; H, 6·2; N, 3·8. $C_{21}H_{23}O_6N$ requires C, 65·5; H, 6·0; N, 3·6%); yield, 9·5 g. (90%).

Ethyl 4-m-*Hydroxyphenyl-lutidine*-3 : 5-*dicarboxylate*.—The foregoing ester (30 g.) and potassium hydroxide (7·5 g.) were heated under reflux in alcohol (250 ml.) for 3 hours. The solvent was removed on the water-bath, and the residue taken up in water and filtered. The clear filtrate was acidified with acetic acid, and the precipitate collected and recrystallised from aqueous alcohol. *Ethyl* 4-m-*hydroxyphenyl-lutidine*-3 : 5-*dicarboxylate* had m. p. 180—181° (Found : C, 66·6; H, 6·3; N, 4·3. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·2; N, 4·1%); yield, 23 g. (88%).

5-*Carbethoxy*-4-m-*hydroxyphenyl-lutidine*-3-*carboxylic acid*, m. p. 279° (from alcohol) (Found : C, 64·9; H, 5·5; N, 4·6. $C_{17}H_{17}O_5N$ requires C, 64·8; H, 5·4; N, 4·5%) (yield, 70%), and *ethyl* 4-m-*hydroxyphenyl-lutidine*-3-*carboxylate*, m. p. 164—165° (from acetone–light petroleum) (Found : C, 70·9; H, 6·4; N, 5·2. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·4; N, 5·2%) (yield, 47%), were also prepared.

Ethyl 4-m-*Methoxyphenyl-lutidine*-3 : 5-*dicarboxylate*.—Ethyl 4-*m*-hydroxyphenyl-lutidine-3 : 5-dicarboxylate (50 g.) was dissolved in a solution of potassium hydroxide (15 g.) in water (500 ml.). The filtered solution was treated with methyl sulphate (25 ml.), added in portions with shaking during 40 minutes. After the mixture had been kept overnight at room temperature the precipitate was collected and crystallised from aqueous alcohol. *Ethyl* 4-m-*methoxyphenyl-lutidine*-3 : 5-*dicarboxylate* melted at 70° (Found : C, 67·0; H, 6·3; N, 4·0. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·4; N, 3·9%) (yield, 50 g.; 94%).

The following were also obtained. 5-*Carbethoxy*-4-m-*methoxyphenyl-lutidine*-3-*carboxylic acid* platelets (from aqueous alcohol), m. p. 195° (Found : C, 65·4; H, 5·9; N, 4·7. $C_{18}H_{19}O_5N$ requires C, 65·6; H, 5·8; N, 4·3%) (yield, 61%); *ethyl* 4-m-*methoxyphenyl-lutidine*-3-*carboxylate*, a nearly colourless viscous oil, b. p. 245°/40 mm. (Found : N, 5·2. $C_{17}H_{19}O_3N$ requires N, 4·9%) (yield, 77%); 4-m-*methoxyphenyl-lutidine*-3-*carboxylic acid*, m. p. 261° (decomp.) (from aqueous spirit) (Found : C, 69·6; H, 6·0; N, 5·6. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·8; N, 5·5%) (yield, 42%); 6(8)-*methoxy*-1 : 3-*dimethyl*-2-*azafluorenone*, faintly yellow crystals [from light petroleum (b. p. 80/100°)], m. p. 141° (Found : C, 75·3; H, 5·4; N, 5·8. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·4; N, 5·9%) (yield, 65%).

6(8)-*Hydroxy*-1 : 3-*dimethyl*-2-*azafluorenone*.—The foregoing compound (2 g.) was heated under reflux with 50% hydrogen bromide (50 ml.) for 1 hour. The yellow hydrobromide was collected and dissolved in sodium hydroxide solution, and the mixture saturated with carbon dioxide. The precipitate was collected and crystallised from alcohol, giving 6(8)-*hydroxy*-1 : 3-*dimethyl*-2-*azafluorenone*, yellow needles, m. p. >300° (Found : C, 75·0; H, 5·1. $C_{14}H_{11}O_2N$ requires C, 74·7; H, 4·9%), in nearly quantitative yield.

4-p-*Methoxyphenyl-lutidine*-3 : 5-*dicarboxylic Acid*.—Ethyl 4-*p*-methoxyphenyl-lutidine-3 : 5-dicarboxylate (55 g.; Hinkel and Madel, *loc. cit.*) was heated under reflux with potassium hydroxide (75 g.) and ethanol (250 ml.) for 3 hours. After the mixture had been set aside at 0° the potassium

salt was collected, dissolved in water, and acidified with 2N-sulphuric acid (70 ml.). The precipitate was collected and recrystallised from dilute acetic acid. 4-p-*Methoxyphenyl-lutidine*-3 : 5-*dicarboxylic acid* formed prismatic needles, m. p. 295—296° (decomp.) (Found : C, 63·8; H, 4·9. $C_{16}H_{15}O_5N$ requires C, 63·8; H, 5·0%).

Also prepared were 5-*carbethoxy*-4-p-*methoxyphenyl-lutidine*-3-*carboxylic acid* octahedra (from aqueous alcohol), m. p. 189·5—191·5° (Found : C, 65·7; H, 5·8. $C_{18}H_{19}O_5N$ requires C, 65·7; H, 5·8%), ethyl 4-*p*-methoxyphenyl-lutidine-3-carboxylate, a faintly yellow viscous oil, b. p. 218—219°/20 mm. (Found : N, 5·2. Calc. for $C_{17}H_{19}O_3N$: N, 4·9%) (cf. Borsche and Hahn, *loc. cit.*), 4-*p*-methoxyphenyl-lutidine-3-carboxylic acid, isolated as the *sulphate*, m. p. 161—162° (from alcohol) (Found : S, 9·8. $C_{15}H_{15}O_3N,H_2SO_4$ requires S, 9·0%) (yield, 51%), 7-methoxy-1 : 3-dimethyl-2-azafluorenone, yellow needles, m. p. 137—138° (from alcohol) (Found : N, 6·2. Calc. for $C_{15}H_{15}O_2N$: N, 5·9%) (Borsche and Hahn, *loc. cit.* give m. p. 131°) (yield, 75%), 7-*hydroxy*-1 : 3-*dimethyl*-2-*azafluorenone*, yellow crystals, m. p. >300° (from alcohol) (Found : C, 74·5; H, 5·1; N, 6·4. $C_{14}H_{11}O_2N$ requires C, 74·7; H, 4·9; N, 6·2%) (yield, nearly quantitative), 5-*carbethoxy*-4-m-*nitrophenyl-lutidine*-3-*carboxylic acid* (prepared from the di-ester; Hinkel, Ayling, and Morgan, *J.*, 1931, 1840), m. p. 220·5° (from aqueous alcohol) (Found : C, 59·3; H, 4·8; N, 8·3. $C_{17}H_{16}O_6N_2$ requires C, 59·3; H, 4·7; N, 8·1%) (yield, 55%), *ethyl* 4-m-*nitrophenyl-lutidine*-3-*carboxylate picrate*, deep-yellow prisms (from methanol), m. p. 160° (Found : N, 13·4. $C_{18}H_{16}O_4N_2,C_6H_3O_7N_3$ requires N, 13·2%) (the base crystallised after many months, forming white needles, m. p. 57°), 4-m-*nitrophenyl-lutidine*-3-*carboxylic acid*, nearly white crystals (from aqueous alcohol), m. p. 263° (decomp.) (Found : N, 10·5. $C_{14}H_{12}O_4N_2$ requires N, 10·3%) (yield, 96%), 5-*carbethoxy*-4-p-*nitrophenyl-lutidine*-3-*carboxylic acid* (prepared from the di-ester; Hinkel, Ayling, and Morgan, *loc. cit.*), yellow needles (from methanol), m. p. 232° (Found : C, 59·3; H, 4·8; N, 8·4. $C_{17}H_{16}O_6N_2$ requires C, 59·3; H, 4·7; N, 8·2%) (yield, 69%), *ethyl* 4-p-*nitrophenyl-lutidine*-3-*carboxylate picrate*, stout yellow needles (from aqueous spirit), m. p. 201—203° (Found : N, 13·5. $C_{18}H_{16}O_4N_2,C_6H_3O_7N_3$ requires N, 13·2%) (yield, 72%), and 4-p-*nitrophenyl-lutidine*-3-*carboxylic acid*, yellow crystals, m. p. 274·5° (from alcohol) (Found : N, 10·5. $C_{14}H_{12}O_4N_2$ requires N, 10·3%) (yield, 95%).

Ethyl 4-p-*Benzamidophenyl-lutidine*-3-*carboxylate*.—Ethyl 4-*p*-nitrophenyl-lutidine-3-carboxylate (5 g.), reduced iron (10 g.), and 70% ethanol (80 ml.) were heated under reflux for 1 hour. The mixture was filtered hot and the filtrate evaporated to dryness on the water-bath under reduced pressure. The glassy residue was dissolved in pyridine (20 ml.) and treated with benzoyl chloride (2·4 g.). After being heated for 1 hour on the water-bath the mixture was diluted with water, and the precipitate collected and crystallised from light petroleum (b. p. 80—100°). *Ethyl* 4-p-*benzamidophenyl-lutidine*-3-*carboxylate* formed platelets, m. p. 144—145° (Found : C, 73·4; H, 5·9; N, 7·6. $C_{23}H_{22}O_3N_2$ requires C, 73·8; H, 5·9; N, 7·5%) (yield, 5 g., 80%).

4-p-*Benzamidophenyl-lutidine*-3-*carboxylic Acid*.—The foregoing ester (75 g.) and potassium hydroxide (12 g.) were heated under reflux in alcohol (300 ml.) for 70 hours. The alcohol was removed on the water-bath, and the residue diluted with water and filtered. The filtrate was acidified with concentrated sulphuric acid (5·7 ml.), and the precipitate collected and crystallised from glacial acetic acid. 4-*p*-Benzamidophenyl-lutidine-3-carboxylic acid separated as the *acetate*, m. p. 318° (decomp.) (Found : C, 67·0; H, 5·4; N, 6·8. $C_{21}H_{18}O_3N_2,CH_3{\cdot}CO_2H$ requires C, 68·0; H, 5·6; N, 6·9%).

Ethyl 4-p-*tolyl-lutidine*-3 : 5-*dicarboxylate*, a pale yellow viscous oil, b. p. 220°/20 mm. (Found : C, 70·4; H, 6·7; N, 4·3. $C_{20}H_{23}O_4N$ requires C, 70·7; H, 7·0; N, 4·3%) (yield, 72%), 5-*carbethoxy*-4-p-*tolyl-lutidine*-3-*carboxylic acid*, m. p. *ca.* 177°, decomp. 230° (from benzene–light petroleum) (Found : C, 69·0; H, 6·5; N, 4·4. $C_{18}H_{19}O_4N$ requires C, 69·1; H, 6·1; N, 4·4%), ethyl 3-acetyl-4-phenyl-lutidine-5-carboxylate [prepared in improved yield by oxidation of the dihydro-ester (Knoevenagel and Rauschhaupt, *Ber.*, 1898, **31**, 1027)], m. p. 88° (from light petroleum) (Found : C, 73·4; H, 6·6; N, 4·5. Calc. for $C_{18}H_{19}O_3N$: C, 72·8; H, 6·4; N, 4·7%) (yield, 80%), and 3-*acetyl*-4-*phenyl-lutidine*-5-*carboxylic acid*, m. p. 264° (decomp.) (from benzene–methanol) (Found : C, 71·9; H, 5·6; N, 5·1. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6; N, 5·2%) (yield, 61%), were also synthesised.

Ethyl 4-(4′-*Acetoxy*-3′-*methoxyphenyl*)*dihydrolutidine*-3 : 5-*dicarboxylate*.—The corresponding 4′-hydroxy-compound (150 g.; Hinkel, Ayling, and Morgan, *J.*, 1935, 817) and acetic anhydride (500 ml.) were warmed on the water-bath for 1 hour. The mixture was poured into water, and the oily precipitate, which solidified when kept, collected and recrystallised from aqueous alcohol. *Ethyl* 4-(4′-*acetoxy*-3′-*methoxyphenyl*)*dihydrolutidine*-3 : 5-*dicarboxylate* formed crystals, m. p. 132—133° (Found : C, 63·1; H, 6·8. $C_{22}H_{27}O_7N$ requires C, 63·4; H, 6·5%); yield, 150 g. (90%).

Ethyl 4-(4′-*Acetoxy*-3′-*methoxyphenyl*)-*lutidine*-3 : 5-*dicarboxylate*.—The foregoing dihydro-compound (87 g.) in acetic acid (200 ml.) was treated with chromium trioxide (14 g.) in acetic acid (100 ml.). The mixture was warmed on the water-bath for 30 minutes, diluted with water, and made alkaline with aqueous ammonia. The precipitate was collected, dried, and recrystallised from light petroleum–acetone. *Ethyl* 4-(4′-*acetoxy*-3′-*methoxyphenyl*)-*lutidine*-3 : 5-*dicarboxylate* melted at 148° (Found : C, 63·3; H, 6·3. $C_{22}H_{25}O_7N$ requires C, 63·6; H, 6·0%); yield, 70 g. (80%).

Ethyl 4-(4′-*Hydroxy*-3′-*methoxyphenyl*)-*lutidine*-3 : 5-*dicarboxylate*.—The foregoing compound (65 g.) in alcohol (500 ml.) was treated with potassium hydroxide (17·5 g.), and the mixture heated under reflux for 1 hour. The solvent was removed on the water-bath, and the residue diluted with water and made acid with acetic acid (17·5 ml.). The oily precipitate, which solidified when kept, was collected and crystallised from aqueous alcohol. *Ethyl* 4-(4′-*hydroxy*-3′-*methoxyphenyl*)-*lutidine*-3 : 5-*dicarboxylate* melted at 160—161° (Found : C, 64·4; H, 6·3. $C_{20}H_{23}O_6N$ requires C, 64·4; H, 6·2%); yield, 58 g. (quantitative).

Ethyl 4-(3′ : 4′-*Dimethoxyphenyl*)-*lutidine*-3 : 5-*dicarboxylate*.—The foregoing hydroxy-compound (45 g.), water (400 ml.), and potassium hydroxide (7·5 g.), were treated with methyl sulphate (11·3 ml.) added in portions with shaking. The precipitate was collected, washed, dried, and crystallised from aqueous alcohol. *Ethyl* 4-(3′ : 4′-*dimethoxyphenyl*)-*lutidine*-3 : 5-*dicarboxylate* formed rhombic plates,

m. p. 101—102° (Found: C, 65·0; H, 6·3. $C_{21}H_{25}O_6N$ requires C, 65·1; H, 6·5%); yield, 41 g. (88%).

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QUEEN MARY COLLEGE, UNIVERSITY OF LONDON, E.1. [*Received, March 26th*, 1949.]

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453. *New Syntheses of Heterocyclic Compounds. Part X. 4-Azafluorenones.*

By V. PETROW, J. SAPER, and B. STURGEON.

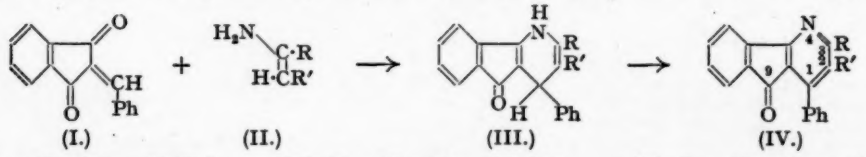
By condensing benzylideneindane-1 : 3-diones with ethyl β-aminocrotonate in glacial acetic acid, numerous *ethyl* 1-*aryl*-3-*methyldihydro*-4-*azafluorenone*-3-*carboxylates* have been prepared; they were oxidised to the corresponding 4-*azafluorenones*. When methyl 2-aminopropenyl ketone, phenyl-2-aminopropenyl ketone, and β-aminocinnamonitrile were employed in place of ethyl β-aminocrotonate in the above synthesis, 2-*acetyl*-1-*phenyl*-3-*methyl*-, 2-*benzoyl*-1-*phenyl*-3-*methyl*-, and 2-*cyano*-1 : 3-*diphenyl*-4-*azafluorenone* were obtained after oxidation.

Attempts to extend the synthesis to the preparation of 1-alkyl-4-azafluorenones were not successful. *Anilomethylindane*-1 : 3-*dione* (VI), prepared by reaction between indane-1 : 3-dione and diphenylformamidine, failed to give a 4-azafluorenone. *Ethyl* 1-2′-*furyl*-3-*methyl*-4-*azafluorenone*-2-*carboxylate* could not be degraded to a compound of the required type.

The *oxime* of ethyl 1-phenyl-3-methyl-4-azafluorenone-2-carboxylate (IV) gave *ethyl* 9-*diacetylamino*-1-*phenyl*-3-*methyl*-4-*azafluorenone*-2-*carboxylate* on reduction, but this compound could be hydrolysed only to the 9-*acetamido*-derivative. Attempts to hydrolyse (IV) to the corresponding acid also failed, concentrated sulphuric acid leading to the formation of 1′-*keto*-3-*methyl*-4-*azaindeno*(3′ : 2′-1 : 2)*fluorenone* (V).

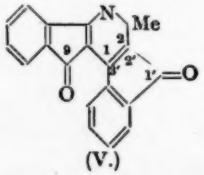
THE preparation of some 4-azafluorenones was undertaken following the observation that certain 1 : 3-dimethyl-2-azafluorenones showed interesting biological properties (preceding paper). 4-Azafluorenones have hitherto been prepared by alkaline oxidation of 7 : 8-benzcinchoninic acids (Doebner and Kuntze, *Annalen*, 1883, **249**, 123), by condensation of indane-1 : 3-dione with *o*-aminobenzaldehyde (Noelting and Blum, *Ber.*, 1901, **34**, 2467) or with ethyl ethoxymethyleneacetoacetate (Errara and Casardi, *Gazzetta*, 1905, **35**, i, 9), or by ring closure of 2-phenylquinoline-3-carboxylic acid (Borsche and Sinn, *Annalen*, 1937, **532**, 146; *ibid*, 1939, **538**, 283). These methods proved unsuitable for extension and we therefore sought an alternative route to this little-studied ring system. Success was finally achieved by a new variation of the Hantzsch collidine synthesis.

Benzaldehyde reacts with indane-1 : 3-dione to give 2-benzylideneindane-1 : 3-dione (I) (Wislicenus and Kotzle, *Annalen*, 1889, **252**, 73). This compound is clearly the cyclic analogue of benzylideneacetylacetone and, like the latter compound (Knoevenagel and Ruschhaupt, *Ber.*, 1898, **31**, 1025), reacts with ethyl 2-aminocrotonate (II) at 100° to give bright-red *ethyl* 1-*phenyl*-3-*methyl*-1 : 4-*dihydro*-4-*azafluorenone*-2-*carboxylate* (III) in less than 30% yield,

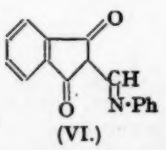


(I.) (II.) (III.) (IV.)

(II; R = Me; R′ = CO_2Et.) (III; R = Me; R′ = CO_2Et.) (IV; R = Me; R′ = CO_2Et.)
(II*a*; R = Me; R′ = COMe.) (III*a*; R = Me; R′ = COMe.) (IV*a*; R = Me; R′ = COMe.)
(II*b*; R = Me; R′ = COPh.) (III*b*; R = Me; R′ = COPh.) (IV*b*; R = Me; R′ = COPh.)
(II*c*; R = Ph; R′ = CN.) (III*c*; R = Ph; R′ = CN.)



(V.)



(VI.)

together with much tar. Reaction in solvents such as ethanol led to the exclusive formation of resins, a result also obtained after addition of basic catalysts such as piperidine. However, in

boiling glacial acetic acid solution ready and rapid condensation took place, giving (III) in nearly quantitative yield; the pure crystalline product generally separated within a few minutes. Other aliphatic acids such as formic and propionic acids can be employed with equal success, but the reaction does not occur in toluene, light petroleum, pyridine, or nitrobenzene. Oxidation of (III) with chromic acid in acetic acid afforded *ethyl* 1-*phenyl*-3-*methyl*-4-*azafluorenone*-2-*carboxylate* (IV) in 90% yield.

In common with other azafluorenones of comparable complexity, (IV) was only slightly basic and could not be converted into a metho-salt (cf. Armit and Robinson, *J.*, 1922, 836). Its hydrolysis, too, proved difficult as the use of alkaline reagents led to secondary changes, whilst warm concentrated sulphuric acid caused hydrolysis and ring closure to 1′-*keto*-3-*methyl*-4-*aza*-*indeno*(3′ : 2′-1 : 2)*fluorenone* (V). (IV) readily formed an *oxime* which, on reduction with zinc dust in acetic anhydride solution, passed smoothly into *ethyl* 9-*diacetylamino*-1-*phenyl*-3-*methyl*-4-*azafluorene*-2-*carboxylate*. Attempts to convert this compound into the 9-amino-derivative by boiling alcoholic hydrochloric acid or by syrupy phosphoric acid at 160° led, however, to the loss of only one acetyl group and the formation of the 9-*acetamido*-derivative, which was remarkably resistant to hydrolysis, a behaviour associated with the sterically sheltered position of the acetamido-group (cf. preceding paper). (IV) failed to undergo the Schmidt reaction which has recently been successfully applied to some 2-azafluorenones (Petrow, *J.*, 1946, 200, 888).

The above synthesis of 1-aryl-4-azafluorenones (IV) has been extended in various ways. Thus various substituted *benzylideneindane*-1 : 3-*diones* have been prepared by direct fusion of the components at 130—140° and condensed with ethyl 2-aminocrotonate (II) in glacial acetic acid. The resulting bright-red *methyl*-, *methoxy*-, and *nitro*-substituted 1-phenyldihydro-4-azafluorenonecarboxylates, obtained in yields of 60—90%, have been converted into the corresponding 4-*azafluorenones* by chromic acid oxidation, and the nitrophenyl derivatives have been reduced to the *amino*-compounds by reduced iron in aqueous ethanol containing a little calcium chloride. *Ethyl* 1-(4′-*hydroxy*-3′-*methoxyphenyl*)-3-*methyl*-1 : 4-*dihydro*-4-*azafluorenone*-2-*carboxylate* had perforce to be acetylated before oxidation. *p*-Dimethylaminobenzylideneindane-1 : 3-dione (Noelting and Blum, *loc. cit.*) condensed normally with ethyl 2-aminocrotonate, but the resulting *ethyl* 1-p-*dimethylaminophenyl*-3-*methyl*-1 : 4-*dihydro*-4-*azafluorenone*-2-*carboxylate* gave only coloured tars on oxidation with chromic acid. Sulphur dehydrogenation, employed by Hinkel and Cremer (*J.*, 1920, 139) with the analogous ethyl 4-*p*-dimethylaminophenyldihydrolutidine-3 : 5-dicarboxylate, also proved unsuccessful. However, warming with dilute nitric acid in alcoholic solution led to simultaneous oxidation and nitration, giving *ethyl* 4-(2′-*nitro*-4′-*dimethylaminophenyl*)-3-*methyl*-4-*azafluorenone*-2-*carboxylate*. The structure assigned to this compound is based on its non-identity with the 3′-*nitro*-isomer prepared from 3′-nitro-4′-dimethylaminobenzylideneindane-1 : 3-dione (Noelting and Blum, *loc. cit.*).

The condensation of *cinnamylideneindane*-1 : 3-*dione* with ethyl 2-aminocrotonate presented certain anomalous features. The characteristic red colour developed normally when the components were heated together under reflux in acetic acid. The only product isolated, albeit in 30% yield, was golden-yellow and, in addition, resistant to chromic acid oxidation unless drastic experimental conditions leading to profound degradation were employed. It has therefore been formulated as an *ethyl* 1-2′-*phenylethyl*-3-*methyl*-4-*azafluorenone*-2-*carboxylate* and presumably results from the initially-formed 1-styryldihydro-derivative by hydrogen transfer.

Ethyl 2-aminocrotonate may frequently be replaced by the "ammonia derivatives" of 1 : 3-diketones in pyridine syntheses of the Hantzsch–Knoevenagel type (Knoevenagel and Ruschhaupt, *loc. cit.*). We therefore examined the reaction of benzylideneindane-1 : 3-dione (I) with methyl 2-aminopropenyl ketone (II*a*) and found, as expected, that smooth condensation took place in glacial acetic acid, giving 2-*acetyl*-1-*phenyl*-3-*methyl*-1 : 4-*dihydro*-4-*azafluorenone* (III*a*), oxidised by chromic acid to the corresponding *pyridine* derivative (IV*a*). *Ethyl* 2-*acetyl*-1-m-*nitrophenyl*- and *ethyl* 2-*acetyl*-1-p-*nitrophenyl*-3-*methyl*-4-*azafluorenone* were likewise prepared and reduced to the corresponding *amino*-compounds.

Condensation of phenyl 2-aminopropenyl ketone (II*b*) with benzylideneindane-1 : 3-dione (I) in glacial acetic acid for 1 hour under reflux resulted in only a 20% yield of the bright-red 2-*benzoyl*-1-*phenyl*-3-*methyl*-1 : 4-*dihydro*-4-*azafluorenone* (III*b*); when the time of heating was prolonged to 2 hours, a bright-yellow product was obtained which was clearly the corresponding 2-*benzoyl*-1-*phenyl*-3-*methyl*-4-*azafluorenone* (IV*b*), as it was also formed by direct oxidation of the foregoing red product (III*b*). The spontaneous loss of hydrogen of some dihydropyridines of similar types has previously been recorded by Michael (*Ber.*, 1885, **18**, 2020).

A further extension of the 4-azafluorenone synthesis was achieved by replacing ethyl

2-aminocrotonate by 2-aminocinnamonitrile (IIc) (cf. Meyer, *J. pr. Chem.*, 1908, **78**, 507), whereupon 2-*cyano*-1 : 3-*diphenyldihydro*-4-*azafluorenone* (IIIc) was readily obtained in good yield.

The above 1-aryl-4-azafluorenones were, in general, too insoluble for adequate biological testing. The possibility of preparing the corresponding 1-alkyl derivatives was therefore examined. The use of aliphatic aldehydes in the above synthesis would clearly furnish the desired 1-alkyl derivatives. Aliphatic aldehydes, however, fail to react with indane-1 : 3-dione in the required manner. Thus Radulescu and Georgescu (*Bull. Soc. chim.*, 1925, **37**, 1069) report that a complex reaction takes place between aliphatic aldehydes and the diketone, leading principally to the formation of the corresponding methylenebisindane-1 : 3-dione. We have nevertheless examined the use of aliphatic aldehydes of somewhat higher molecular weight in the hope that their greater complexity would have some influence on the course of the reaction. All attempts to condense indane-1 : 3-dione with *n*-heptaldehyde, crotonaldehyde, or chloral under a variety of experimental conditions failed to give products of the required type.

The preparation of 2-acetyl- and 2-formyl-indane-1 : 3-dione has previously been reported in the literature and it is apparent that these compounds would form valuable intermediates for the synthesis of the required 4-azafluorenones. In our hands the condensation of diethyl phthalate with acetone in the presence of sodium ethoxide, as described by Schwirin (*Ber.*, 1894, **27**, 105), led to a variety of products in low yield, none of which appeared identical with the acetylindane-1 : 3-dione described in the literature. Attempts to synthesis 2-propionyl- and 2-benzoyl-indanediones were likewise unsuccessful. The preparation of 2-formylindane-1 : 3-dione, reported by Errara (*Gazzetta*, 1902, **32**, 330; 1903, **33**, i, 417) could not be repeated, nor could this compound be obtained by the action of amyl formate and sodium upon indane-1 : 3-dione in ether. These failures must be attributed to the highly reactive character of these intermediates and their consequent tendency to undergo auto-condensation in the alkaline environment necessary for their preparation. The disadvantages inseparable from these methods were nevertheless overcome, and 2-*anilomethylindane*-1 : 3-*dione* (*i.e.*, *formylindane*-1 : 3-*dione anil*) (VI) was prepared in excellent yield by direct condensation of indane-1 : 3-dione with diphenylformamidine at 145°. This elegant reaction, discovered by Piggott and Rodd (B.P. 344,409), has been widely employed, for the introduction of the formyl group, in cyanine dye chemistry. Anilomethylindane-1 : 3-dione (VI), however, failed to react with ethyl 2-aminocrotonate on fusion at 140°, in boiling alcohol in the presence of piperidine, or in boiling acetic anhydride, a failure which cannot be attributed to the employment of the anil, *per se*, as Borsche, Barthenheier, and Wagner-Roemnick (*Annalen*, 1942, **550**, 160) have shown that anils may be advantageously employed in place of the aldehydes in certain quinoline and naphthyridine syntheses. As these attempts to prepare a 1-alkyl-4-azafluorenone proved abortive, an indirect approach was attempted, by way of *ethyl* 1-2′-*furyl*-3-*methyl*-4-*azafluorenone*-2-*carboxylate*. This compound was readily prepared from *furfurylideneindane*-1 : 3-*dione*, followed by oxidation of the resulting *dihydro*-base with nitric acid in alcoholic solution. Unfortunately all attempts at the degradation of the furan ring of this compound, either by prolonged heating with concentrated hydrochloric acid in glacial acetic acid, or by oxidation with chromic acid in sulphuric acid, failed to give compounds of the required type.

Experimental.

M. p.s are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

Substituted Benzylideneindane-1 : 3-*diones, etc.*—Indane-1 : 3-dione (0·1 mol.) and the appropriate aldehyde (0·1 mol.) were fused together at 130—140° in an oil-bath. Water vapour was vigorously evolved and the melt generally solidified after 10—20 minutes. Heating was then continued for a further 15 minutes, whereafter the product was isolated by crystallisation from acetic acid (charcoal). The benzylidene compounds listed in Table I were thus prepared as were the two following compounds.

2-*Cinnamylideneindane*-1 : 3-*dione*, golden needles (70%) (from alcohol), m. p. 161—162° (Found : C, 82·7; H, 4·7. $C_{18}H_{12}O_2$ requires C, 83·1; H, 4·6%).

2-2′-*Furfurylideneindane*-1 : 3-*dione*, small needles (43%) (from acetic acid), m. p. 209—210° (Found : C, 75·7; H, 3·7. $C_{14}H_8O_3$ requires C, 75·0; H, 3·6%).

Ethyl 1-*Phenyl*-3-*methyl*-1 : 4-*dihydro*-4-*azafluorenone*-2-*carboxylate* (III).—(*a*) Benzylideneindane-1 : 3-dione (3·9 g.) and ethyl β-aminocrotonate (2·1 g.) were fused together at 100° for 8 hours. The solid product was extracted with alcohol, and the insoluble residue recrystallised from acetic acid. *Ethyl* 1-*phenyl*-3-*methyl*-1 : 4-*dihydro*-4-*azafluorenone*-2-*carboxylate* (1·8 g., 31%) separated in dark-red plates, m. p. 252—254° (Found : C, 76·1; H, 5·5; N, 4·1. $C_{22}H_{19}O_2N$ requires C, 76·5; H, 5·5; N, 4·1%).

(*b*) A solution of benzylideneindane-1 : 3-dione (5·3 g.) in acetic acid (25 ml.) was treated at the b. p. with ethyl β-aminocrotonate (6·5 g.). A deep-red colour immediately developed, followed after a minute's boiling by the separation of (III) in dark-red plates (6·8 g., 87%), m. p. 251—252°.

The dihydro-compounds listed in Tables II and III were similarly prepared.

TABLE I.

Substituted Benzylideneindane-1 : 3-diones.

Substituent.	M. p.	Yield.	Formula.	%.	C.	H.	N.	Description.
4′-*Methyl*-	154·5—155°	50%	$C_{17}H_{12}O_2$	Found	82·5	5·0	—	Buff-coloured
				Reqd.	82·3	4·8	—	needles (*a*)
2′-*Methoxy*-	167·5—168	69	$C_{17}H_{12}O_3$	Found	77·3	4·5	—	Bright-yellow needles
				Reqd.	77·3	4·5	—	
3′-*Methoxy*-	143	71	$C_{17}H_{12}O_3$	Found	76·8	4·4	—	Peach-coloured
				Reqd.	77·3	4·5	—	needles
4′-*Methoxy*-	158	70	$C_{17}H_{12}O_3$	Found	77·1	4·5	—	Orange needles
				Reqd.	77·3	4·5	—	
3′-Nitro-	250·5	59	$C_{16}H_9O_4N$	Found	68·6	3·1	5·1	Cream-coloured
				Calc.	68·8	3·2	5·0	needles (*b*)
4′-*Nitro*-	231 (decomp.)	67	$C_{16}H_9O_4N$	Found	69·1	3·2	5·0	Lemon-coloured
				Reqd.	68·8	3·2	5·0	needles
4′-Dimethylamino-	203·5	70	$C_{18}H_{15}O_2N$	Found	77·6	5·7	5·4	Bronze-red needles (*c*)
				Calc.	78·0	5·7	5·4	

(*a*) Recrystallised from light petroleum.
(*b*) Radulescu and Georgescu (*loc. cit.*) give m. p. 246°.
(*c*) Recrystallised from large volumes of alcohol. Noelting and Blum (*loc. cit.*) record m. p. 99°.

Ethyl 1-*Phenyl*-3-*methyl*-4-*azafluorenone*-2-*carboxylate*.—The foregoing dihydro-compound (4·2 g.), dissolved in warm acetic acid (120 ml.), was treated with chromic acid (1·2 g.) in water. After 5 minutes the solution was diluted with water until the product began to separate. *Ethyl* 1-*phenyl*-3-*methyl*-4-*azafluorenone*-2-*carboxylate* (3·8 g., 88%) (IV) crystallised from aqueous spirit in flat, lemon needles, m. p. 174·5—175·5° (Found : C, 77·4; H, 5·1; N, 4·2. $C_{22}H_{17}O_3N$ requires C, 77·0; H, 5·0; N, 4·1%). The *oxime* separated from large volumes of alcohol in silver platelets, m. p. 281° (decomp.) (Found : C, 73·9; H, 5·3; N, 7·5. $C_{22}H_{18}O_3N_2$ requires C, 73·7; H, 5·0; N, 7·8%).

Other compounds similarly prepared are listed in Tables II and III.

1′-*Keto*-3-*methyl*-4-*azaindeno*(3′ : 2′-1 : 2)*fluorenone* (V) (with Mr. A. COURTS).—Ethyl 1-phenyl-3-methyl-4-azafluorenone-2-carboxylate (2 g.) was dissolved in concentrated sulphuric acid (20 ml.), and the solution maintained at 60° for 5 minutes. The yellow solid which separated on pouring the mixture on ice was collected and recrystallised from acetic acid, giving the *diketone* (V) in yellow needles, m. p. 263° (Found : C, 80·8; H, 4·0; N, 4·4 $C_{20}H_{11}O_2N$ requires C, 80·8; H, 3·7; N, 4·7%).

Ethyl 9-*diacetylamino*-1-*phenyl*-3-*methyl*-4-*azafluorene*-2-*carboxylate*, colourless octahedra, m. p. 135°, from ligroin (Found : C, 72·9; H, 5·6; N, 7·0. $C_{26}H_{24}O_4N_2$ requires C, 72·9; H, 5·6; N, 6·5%), was obtained by reduction of the above-mentioned oxime with zinc dust and acetic anhydride as described in the preceding communication. Hydrolysis of this compound (2·7 g.) with alcohol (15 ml.) and concentrated hydrochloric acid (30 ml.) under reflux for 1 hour, followed by precipitation with dilute aqueous ammonia, gave *ethyl* 9-*acetamido*-1-*phenyl*-3-*methyl*-4-*azafluorene*-2-*carboxylate* as octahedra (from benzene–ligroin), m. p. 196° (Found : C, 74·7; H, 5·9; N, 7·8; Ac, 11·6. $C_{24}H_{22}O_3N_2$ requires C, 74·6; H, 5·7; N, 7·3; Ac, 11·1%), in almost theoretical yield. The compound was recovered unchanged after being heated at 190° with syrupy phosphoric acid.

Ethyl 1-p-*Dimethylaminophenyl*-3-*methyl*-1 : 4-*dihydro*-4-*azafluorenone*-2-*carboxylate*.—This *compound* (40% yield) formed orange needles from aqueous alcohol (charcoal), m. p. 170° (Found : C, 74·5; H, 6·1; N, 7·3. $C_{24}H_{24}O_2N_2$ requires C, 74·2; H, 6·2; N, 7·2%). Treatment of a boiling alcoholic solution of it (1·5 g.) with nitric acid (2·5 ml.; *d* 1·4), followed by precipitation with dilute aqueous ammonia gave *ethyl* 1-(2′-*nitro*-4′-*dimethylaminophenyl*)-3-*methyl*-4-*azafluorenone*-2-*carboxylate*, which formed felted deep-yellow needles, m. p. 179°, from benzene–ligroin (Found : C, 67·2; H, 4·9; N, 9·8. $C_{24}H_{21}O_4N_3$ requires C, 66·8; H, 4·9; N, 9·7%). The compound gave a depression in m. p. in admixture with the isomeric 3′-nitro-compound (Table II).

Ethyl 1-2′-*Phenylethyl*-3-*methyl*-4-*azafluorenone*-2-*carboxylate*.—A solution of cinnamylideneindane-1 : 3-dione (5 g.) in acetic acid (20 ml.) was treated with ethyl 2-aminocrotonate (5 g.). The oil which separated on adding water to the red solution was purified initially from alcohol (charcoal) and finally from *n*-hexane, giving *ethyl* 1-2′-*phenylethyl*-3-*methyl*-4-*azafluorenone*-2-*carboxylate* (17%) in thin golden needles, m. p. 139—140° (Found : C, 77·8; H, 5·4; N, 3·8. $C_{24}H_{21}O_2N$ requires C, 77·6; H, 5·7; N, 3·8%). The compound was recovered unchanged after treatment with chromic acid in acetic acid. The yield was not improved by heating the reaction mixture under reflux, or by carrying out the condensation in boiling acetic anhydride.

2-*Benzoyl*-1-*phenyl*-3-*methyl*-1 : 4-*dihydro*-4-*azafluorenone*.—Benzylideneindane-1 : 3-dione (4·2 g.), phenyl 2-aminopropenyl ketone (5·5 g.; Knoevenagel, *Ber.*, 1903, **36**, 2187), and acetic acid (35 ml.) were heated under reflux. The characteristic red colour developed only after 10—15 minutes, and heating was therefore continued for 1 hour. Addition of water precipitated a dark-red oil which, when recrystallised from aqueous alcohol (charcoal), gave carmine platelets of 2-*benzoyl*-1-*phenyl*-3-*methyl*-1 : 4-*dihydro*-4-*azafluorenone* (22%), m. p. 166—167° (Found : N, 3·9. $C_{28}H_{19}O_2N$ requires N, 3·7%).

2-*Benzoyl*-1-*phenyl*-3-*methyl*-4-*azafluorenone*.—(*a*) Benzylideneindane-1 : 3-dione (3·4 g.), phenyl 2-aminopropenyl ketone (4·0 g.), and acetic acid (25 ml.) were heated under reflux for 2 hours. Isolation of the product as described above gave 2-*benzoyl*-1-*phenyl*-3-*methyl*-4-*azafluorenone* (18%), lemon-yellow needles, m. p. 175°, from benzene–ligroin (Found : C, 82·9; H, 4·5; N, 3·9. $C_{28}H_{17}O_2N$ requires C, 83·2; H, 4·5; N, 3·7%). The compound gave a depression of the m. p. in admixture with the preceding dihydro-compound.

(*b*) The corresponding dihydro-compound was oxidised with chromic acid in the usual manner. The

TABLE II.

Ethyl 3-Methyl-4-azafluorenone-2-carboxylates.

Substituent.	M. p.	Yield.	Formula.	%.	C.	H.	N.	Description.	Solvent.
1-p-*Tolyl*-1 : 4-*dihydro*-	237·5—238·5°	70%	$C_{23}H_{21}O_3N$	Found	77·1	5·9	4·0	Deep-red platelets	*b*
				Reqd.	76·9	5·9	3·9		
1-p-*Tolyl*-	118	—	$C_{23}H_{19}O_3N$	Found	77·2	5·1	4·0	Ivory-coloured needles	*f*
				Reqd.	77·3	5·3	3·9		
1-o-*Methoxyphenyl*-1 : 4-*dihydro*-	211·5—213	60	$C_{23}H_{21}O_4N$	Found	73·6	5·5	3·9	Plum-coloured crystals	*b*
				Reqd.	73·6	5·6	3·7		
1-o-*Methoxyphenyl*-	165·5—166	—	$C_{23}H_{19}O_4N$	Found	74·0	5·2	3·5	Pale-yellow warts	*f*
				Reqd.	74·0	5·1	3·8		
1-m-*Methoxyphenyl*-1 : 4-*dihydro*-	223—224	93	$C_{23}H_{21}O_4N$	Found	73·5	5·6	3·9	Scarlet small plates	*c*
				Reqd.	73·6	5·6	3·7		
1-m-*Methoxyphenyl*-	115—116	—	$C_{23}H_{19}O_4N$	Found	74·4	5·0	3·8	Pale-yellow crusts	*f*
				Reqd.	74·0	5·1	3·8		
1-p-*Methoxyphenyl*-1 : 4-*dihydro*-	253	74	$C_{23}H_{21}O_4N$	Found	73·4	5·6	4·0	Dark-red plates	*b*
				Reqd.	73·6	5·6	3·7		
1-p-*Methoxyphenyl*-	120·5	—	$C_{23}H_{19}O_4N$	Found	73·5	5·0	3·8	Bright-yellow prisms	*f*
				Reqd.	74·0	5·1	3·8		
1-(3′ : 4′-*Methylenedioxyphenyl*)-1 : 4-*dihydro*-	275	70	$C_{23}H_{19}O_5N$	Found	71·1	5·1	3·7	Deep-red plates	*b*
				Reqd.	71·0	4·9	3·6		
1-(3′ : 4′-*Methylenedioxyphenyl*)-	121·5	—	$C_{23}H_{17}O_5N$	Found	71·2	4·4	—	Mustard-coloured prisms	*f*
				Reqd.	71·3	4·4	—		
1-(4′-*Hydroxy*-3′-*methoxyphenyl*)-1 : 4-*dihydro*-	232·5—233	64	$C_{23}H_{21}O_5N$	Found	—	—	3·6	Deep-red needles	*a*
				Reqd.	—	—	3·6		
1-(4′-*Acetoxy*-3′-*methoxyphenyl*)-1 : 4-*dihydro*-	201—202	—	$C_{25}H_{23}O_6N$	Found	69·6	5·3	3·5	Scarlet platelets	*d*
				Reqd.	69·3	5·3	3·2		
1-(4′-*Acetoxy*-3′-*methoxyphenyl*)-	151	—	$C_{23}H_{21}O_6N$	Found	69·5	4·9	3·3	Fine cream-coloured needles	*e*
				Reqd.	69·6	4·9	3·3		
1-m-*Nitrophenyl*-1 : 4-*dihydro*-	241 (decomp.)	79	$C_{22}H_{18}O_5N_2$	Found	67·6	4·7	7·3	Flat dark-red needles	*b*
				Reqd.	67·7	4·6	7·2		
1-m-*Nitrophenyl*-	168	—	$C_{22}H_{16}O_5N_2$	Found	68·1	4·6	7·5	Felted ivory-coloured needles	*f*
				Reqd.	68·0	4·1	7·2		
1-m-*Aminophenyl*-	201—203	—	$C_{22}H_{18}O_3N_2$	Found	73·7	5·1	7·5	Ochre-coloured crystals	*e*
				Reqd.	73·7	5·0	7·8		
1-p-*Nitrophenyl*-1 : 4-*dihydro*-	226·5—227·5	84	$C_{22}H_{18}O_5N_2$	Found	67·4	4·5	6·8	Scarlet needles	*c*
				Reqd.	67·7	4·6	7·2		
1-p-*Nitrophenyl*-	201—201·5	—	$C_{22}H_{16}O_5N_2$	Found	67·8	3·1	7·5	Yellowish-green needles	*e*
				Reqd.	68·0	4·1	7·2		
1-p-*Aminophenyl*-	231—232	—	$C_{22}H_{18}O_3N_2$	Found	74·4	5·3	7·8	Deep-orange prisms	*e*
				Reqd.	73·7	5·0	7·8		
1-p-*Dimethylaminophenyl*-1 : 4-*dihydro*-	170	40	$C_{24}H_{24}O_3N_2$	Found	74·5	6·1	7·3	Orange needles	*a*
				Reqd.	74·2	6·2	7·2		
1-(3′-*Nitro*-4′-*dimethylaminophenyl*)-1 : 4-*dihydro*-	227·5—228·5	45	$C_{24}H_{23}O_5N_3$	Found	66·1	5·6	10·0	Scarlet needles	*c*
				Reqd.	66·5	5·3	9·7		
1-(3′-*Nitro*-4′-*dimethylaminophenyl*)-	210	—	$C_{24}H_{21}O_5N_3$	Found	66·5	4·6	9·9	Mustard-coloured prisms	*e*
				Reqd.	66·8	4·9	9·7		
1-2′-*Furyl*-1 : 4-*dihydro*-	249—251	71	$C_{20}H_{17}O_4N$	Found	71·3	4·9	4·1	Dark-red plates	*a*
				Reqd.	71·7	5·1	4·2		
1-2′-*Furyl*-	141—142	—	$C_{20}H_{15}O_4N$	Found	71·8	4·4	4·4	Straw-coloured needles	*f*
				Reqd.	72·1	4·5	4·2		

a, Alcohol. *b*, Acetic acid. *c*, Aqueous acetic acid. *d*, Benzene. *e*, Benzene–ligroin. *f*, Light petroleum.

product formed cream-coloured needles, identical in m. p. and mixed m. p. with the compound obtained by method (*a*).

2-*Cyano*-1 : 3-*diphenyl*-1 : 4-*dihydro*-4-*azafluorenone*.—This compound, fine orange-red needles, m. p. 251° (Found : N, 7·6. $C_{21}H_{16}ON_2$ requires N, 7·4%), from acetic acid, was prepared (40%) by heating benzylideneindane-1 : 3-dione (4 g.), 2-aminocinnamonitrile (5 g.), and acetic acid (40 ml.) under reflux for 30 minutes. 2-*Cyano*-1 : 3-*diphenyl*-4-*azafluorenone* separated in felted cream needles, m. p. 273·5°, from pyridine–ligroin (Found : C, 83·4; H, 4·1; N, 8·1. $C_{25}H_{14}ON_2$ requires C, 83·8; H, 3·9; N, 7·8%).

2-*Anilomethylindane*-1 : 3-*dione*.—Indane-1 : 3-dione (2·1 g.) and diphenylformamidine (3·2 g.) were fused together at 145° for 45 minutes. The crystalline product was washed free from a blue impurity with cold alcohol, and the residue recrystallised from alcohol. 2-*Anilomethylindane*-1 : 3-*dione* (60%) separated in olive-green plates, m. p. 197—198° (Found : C, 77·1; H, 4·4; N, 5·6. $C_{16}H_{11}O_2N$ requires C, 77·1; H, 4·4; N, 5·6%).

TABLE III.

2-Acetyl-3-methyl-4-azafluorenones.

Substituent.	M. p.	Yield.	Formula.	%.	C.	H.	N.	Description.	Solvent.*
1-*Phenyl*-1 : 4-*dihydro*-	246—247°	60%	$C_{21}H_{17}O_2N$	Found	79·9	5·2	4·3	Scarlet needles	
				Reqd.	80·0	5·4	4·4		
1-*Phenyl*-	167·5—168	—	$C_{21}H_{15}O_2N$	Found	80·1	5·0	4·6	Long cream-coloured needles	*f*
				Reqd.	80·5	4·8	4·5		
1-m-*Nitrophenyl*-1 : 4-*dihydro*-	232	88	$C_{21}H_{16}O_4N_2$	Found	69·6	4·7	7·9	Vermilion needles	*a*
				Reqd.	70·0	4·4	7·8		
1-m-*Nitrophenyl*-	224	—	$C_{21}H_{14}O_4N_2$	Found	70·0	4·3	7·8	Ochre-coloured plates	*c*
				Reqd.	70·4	3·9	7·8		
1-m-*Aminophenyl*-	216·5—217·5	—	$C_{21}H_{16}O_2N_2$	Found	76·6	5·2	8·6	Ochre-coloured crystals	*e*
				Reqd.	76·8	4·9	8·5		
1-p-*Nitrophenyl*-1 : 4-*dihydro*-	242·5—243	77	$C_{21}H_{16}O_4N_2$	Found	70·0	4·6	7·9	Strawberry-coloured plates	*b*
				Reqd.	70·0	4·4	7·8		
1-p-*Nitrophenyl*-	238	—	$C_{21}H_{14}O_4N_2$	Found	70·3	4·2	7·6	Pale-yellow needles	*c*
				Reqd.	70·4	3·9	7·8		
1-p-*Aminophenyl*-	253—254	—	$C_{21}H_{16}O_2N_2$	Found	76·8	5·4	8·2	Flame-coloured needles	*a*
				Reqd.	76·8	4·9	8·5		

* See footnote to Table II.

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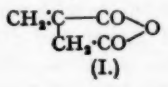
454. *The Friedel–Crafts Reaction with Itaconic Anhydride. 6-Phenyl-4-methyl-3-pyridazone.*

By S. DIXON, HILDA GREGORY, and L. F. WIGGINS.

The reaction of itaconic acid with benzene under Friedel–Crafts conditions has been investigated. The product of the reaction has been shown to be β-benzoyl-α-methylacrylic acid by a study of the absorption spectrum of it and allied compounds, and by synthetic methods. This product has been converted into 6-phenyl-4-methyl-3-pyridazone, which has been synthesised from the β-benzoyl*iso*butyric acid obtained by the Friedel–Crafts reaction of methylsuccinic anhydride and benzene.

THE observation (Lockwood and Ward, *Ind. Eng. Chem.*, 1945, **37**, 403) that itaconic acid may be obtained by the growth of certain micro-organisms, in particular *Aspergillus terreus*, on solutions of glucose or sucrose makes this substance more readily available than hitherto. Since we have been concerned with the study of materials readily obtainable from sucrose we have turned our attention to itaconic acid. In this paper the reaction of the itaconic anhydride with benzene under the conditions of the Friedel–Crafts reaction and the pyridazine derivatives obtained by condensation of the product of this reaction with hydrazine have been investigated.

When itaconic anhydride (I) is treated with benzene and aluminium chloride in a typical Friedel–Crafts reaction, a crystalline compound (*A*), m. p. 155°, is obtained. This contains a phenyl, a carbonyl, and a carboxyl group, but no halogen atoms. It affords a *semicarbazone*, and analysis of the compound and its semicarbazone show its empirical formula to be $C_{11}H_{10}O_3$.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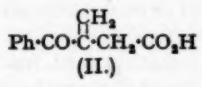
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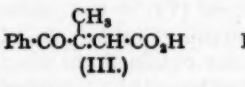
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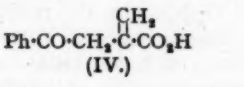
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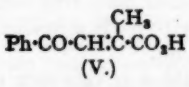
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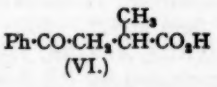
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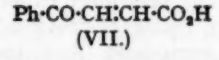
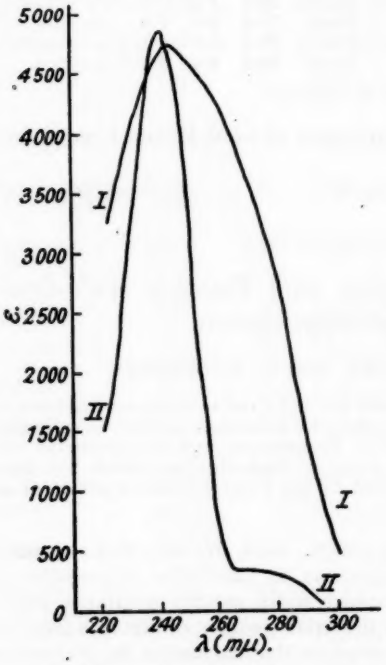

(VII.)

By the method of synthesis employed, (*A*) may have any of the structures (II)—(V). (III) and (V) are fully conjugated structures, whereas (II) and (IV) are not. Hence there should be a marked difference in the absorption spectra of these two types. The Friedel–Crafts condensation of benzene with maleic anhydride gives the well-known β-benzoylacrylic acid (VII). The absorption spectrum of this would be expected to be very similar to that shown by structures (III) or (V). Compound (*A*) and β-benzoylacrylic acid did indeed exhibit similar absorption

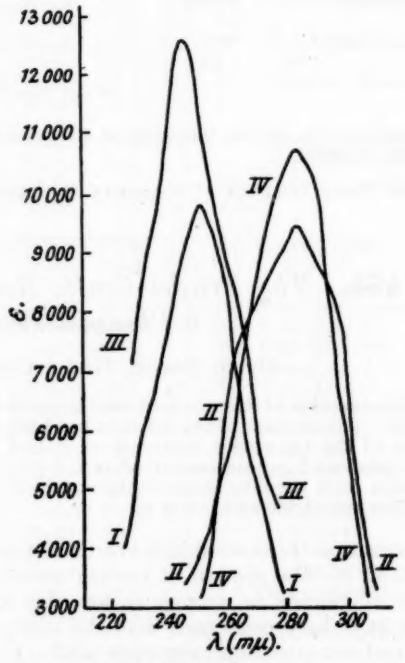
spectra; the former showed maximum absorption of light in the ultra-violet region at 2425 A., and the latter at 2450 A. (see Fig. 1). Thus compound (*A*) is represented by (III) or (V). Furthermore, hydrolysis with barium hydroxide yielded acetophenone, characterised as its semicarbazone, which suggests that (*A*) cannot be represented by structures (II) and (III). In conjunction with the absorption spectra data quoted above, this indicates that compound (*A*) is β-benzoyl-α-methylacrylic acid (V), which is confirmed by hydrogenation under mild conditions with a palladium catalyst. The product was the crystalline β-benzoyl*iso*butyric acid (VI) which was synthesised by Klobb (*Bull. Soc. chim.*, 1897, [iii], **17**, 408) by the condensation of ω-bromoacetophenone with ethyl sodiocyanoacetate, treatment of the sodium derivative of the product with methyl iodide, and hydrolysis with sodium hydroxide. A better proof of the constitution of this material was later provided by Oppenheim (*Ber.*, 1901, **34**, 4227), who synthesised it starting from ω-bromoacetophenone and ethyl sodiomethylmalonate.

FIG. 1.



I. β-*Benzoylacrylic acid.*
II. β-*Benzoyl-α-methylacrylic acid.*

FIG. 2.



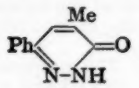
I. 6-*Phenyl-3-pyridazone.*
II. 6-*Phenyl-3-pyridazinone.*
III. *Condensation product of compound "A" with hydrazine.*
IV. 6-*Phenyl-4-methyl-3-pyridazinone.*

(*Measurements carried out in ethyl alcohol solution.*)

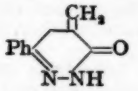
Oppenheim also prepared (VI) by the condensation of methylsuccinic anhydride with benzene in the presence of aluminum chloride. In addition to the α-methyl acid Mayer and Stamm (*Ber.*, 1923, **56**, 1424) later obtained the isomeric β-methyl acid from this reaction. During our preparation of (VI) by Oppenheim's method, we found that methylsuccinic acid was obtained from itaconic acid more expeditiously (and in 82% yield) by catalytic hydrogenation than by the sodium amalgam previously used (Fittig, *Annalen*, 1898, **304**, 156).

If the compound (*A*) is indeed represented by (V) it should yield a pyridazone derivative (VIII) on treatment with hydrazine. This transformation has now been accomplished, although in poor yield (11%). If the compound (*A*) had the methylene structure (IV) this reaction would, of course, lead to a pyridazinone (IX). If, however, prototropic change occurred during the condensation with hydrazine, then the pyridazone (VIII) might also be formed from (IV). It has been observed that pyridazone and pyridazinone derivatives absorb light characteristically in the ultra-violet region of the spectrum, and, moreover, that there is a marked difference

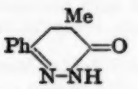
in the light absorption of pyridazone and pyridazinone derivatives. 6-Phenyl-3-pyridazone shows one absorption peak at 2515 A., whereas the corresponding pyridazinone derivative shows



(VIII.)



(IX.)



(X.)

maximum absorption at 2840 A. The product of the condensation of compound (*A*) with hydrazine shows an absorption spectrum with the head of the band at 2475 A. and hence closely resembles the pyridazone (see Fig. 2). If the possibilities of prototropic change are discounted, these observations provide further evidence that compound (*A*) is β-benzoyl-α-methylacrylic acid (V). The true 6-phenyl-4-methyl-3-pyridazinone (X) was obtained when β-benzoyl*iso*-butyric acid was condensed with hydrazine. This showed maximum absorption of light in the ultra-violet region at 2840 A. and was dehydrogenated by bromine (Overend and Wiggins, *J.*, 1946, 239) to give 6-phenyl-4-methyl-3-pyridazone, identical with that obtained by the condensation of compound (*A*) with hydrazine.

The formation of pyridazone derivatives from γ-keto-acids containing an αβ-unsaturated linkage is always difficult. We have observed this in the case of acetyl- and benzoyl-acrylic acids in addition to the case just described. It would appear, therefore, that these compounds are essentially *trans*-isomers and that conversion into the *cis*-form must take place before cyclisation to a pyridazone derivative.

Some confusion exists in the literature as to the course of the reaction of benzene and citraconic acid anhydride in the presence of aluminium chloride; von Pechmann (*Ber.*, 1882, **15**, 833) obtained β-benzoyl-β-methylacrylic acid, m. p. 113°, and proved its constitution by hydrolysis to propiophenone and glyoxylic acid. On the other hand, Bogert and Ritter (*J. Amer. Chem. Soc.*, 1925, **47**, 526) obtained an acid, m. p. 153°, which was shown to be β-benzoyl-α-methylacrylic acid and is clearly identical with the compound obtained during the work described in this paper. Thus, it would appear that the reaction of citraconic anhydride with benzene can take place in either of the possible directions.

Experimental.

Condensation of Itaconic Anhydride with Benzene in the Presence of Aluminium Chloride.—Itaconic anhydride (28 g.), prepared by the distillation of the acid with phosphoric oxide, was dissolved in dry benzene (200 c.c.) and treated with finely powdered anhydrous aluminium chloride (70 g.). On slight warming of the mixture a vigorous reaction occurred, much hydrogen chloride being evolved. Heating under reflux was continued for 3 hours. The mixture was cooled and the excess of aluminium chloride decomposed by carefully adding dilute hydrochloric acid. Benzene was removed by distillation with steam, and a pale yellow solid remained. This, β-benzoyl-α-methylacrylic acid, was collected and recrystallised from alcohol–water, forming long needles (37 g., 78%), m. p. 155° (Bogert and Ritter, *loc. cit.*, recorded m. p. 153°) (Found: C, 69·0; H, 5·35. Calc. for $C_{11}H_{10}O_3$: C, 69·4; H, 5·21%). Treatment of the acid, dissolved in cold alcohol–water, with an aqueous solution of semicarbazide hydrochloride and sodium acetate afforded the *semicarbazone* which, recrystallised from absolute alcohol, formed needles, m. p. 218° (Found: C, 58·2; H, 5·49; N, 16·9. $C_{12}H_{13}O_3N_3$ requires C, 58·3; H, 5·26; N, 17·0%).

Condensation of β-Benzoyl-α-methylacrylic Acid with Hydrazine. 6-Phenyl-4-methyl-3-pyridazone.—β-Benzoyl-α-methylacrylic acid (18 g.), dissolved in hot N-sodium hydroxide solution (90 c.c.), was treated with a solution of hydrazine sulphate (12·5 g.), also dissolved in N-sodium hydroxide solution (90 c.c.). The mixture was heated on a water-bath for 2 hours, an oil appearing in the mixture. On cooling, the oil partly crystallised. The supernatant aqueous layer was decanted and the semi-solid mass dissolved in hot alcohol–water, filtered with charcoal, and allowed to crystallise. The pale yellow crystals of 6-*phenyl*-4-*methyl*-3-*pyridazone*, recrystallised from alcohol–water, formed plates, m. p. 189° (2·0 g., 11·4%) (Found: C, 70·5; H, 5·4; N, 15·4. Calc. for $C_{11}H_{10}ON_2$: C, 71·0; H, 5·38; N, 15·1%).

Alkaline Hydrolysis of β-Benzoyl-α-methylacrylic Acid.—β-Benzoyl-α-methylacrylic acid (2 g.) was heated at 80° for 4 hours with barium hydroxide octahydrate (7 g.) in water (60 c.c.). The mixture was steam-distilled and the distillate extracted with ether. The extract was dried ($MgSO_4$) and evaporated to an oil. A small amount of this was dissolved in alcohol and treated with an aqueous solution of semicarbazide hydrochloride and sodium acetate. After being heated for 2 minutes, the solution was allowed to cool, whereupon a crystalline solid separated. This, recrystallised from absolute alcohol, showed m. p. 198° alone or in admixture with an authentic specimen of acetophenone semicarbazone.

Reduction of β-Benzoyl-α-methylacrylic Acid.—β-Benzoyl-α-methylacrylic acid (2 g.) was dissolved in methanol (25 c.c.) and subjected to hydrogenation over palladium–charcoal at room temperature under a slight pressure of hydrogen. Absorption proceeded rapidly until the theoretical amount of hydrogen necessary for the saturation of the olefinic linkage (250 c.c.) had been absorbed. The hydrogenation was arrested, the catalyst filtered off, and the clear solution evaporated to dryness. β-Benzoyl-*iso*butyric acid, recrystallised three times from dilute alcohol, formed needles, m. p. 140° alone or in admixture with an authentic specimen (yield, 1·8 g., 90%).

Hydrogenation of Itaconic Acid.—Itaconic acid (100 g.) in water (600 c.c.) was shaken in an autoclave with hydrogen under pressure in the presence of Raney nickel at room temperature. When absorption of hydrogen had ceased, the solution was filtered and evaporated to dryness. A pale green solid remained which was extracted with benzene–ether. The extract, on evaporation of the solvent, yielded a white crystalline solid which, recrystallised from benzene–ether, formed prisms, m. p. 111°, of methylsuccinic acid (82 g., 82%).

β-Benzoylisobutyric Acid.—Methylsuccinic anhydride (37 g.), m. p. 37°, prepared by treatment of methylsuccinic acid with acetyl chloride, was dissolved in dry benzene (185 g.) and mixed, with cooling, with finely ground anhydrous aluminium chloride (74 g.). The mixture was heated under reflux on a water-bath for 2 hours. An excess of aluminium chloride was then decomposed with dilute hydrochloric acid, and the benzene removed by steam-distillation. A white solid remained which, recrystallised from alcohol–water, formed long colourless needles, m. p. 140° (37 g., 60%). Oppenheim (*loc. cit.*) records the same m. p.

6-Phenyl-4-methyl-3-pyridazinone.—β-Benzoylisobutyric acid (37 g.) in N-sodium hydroxide solution (190 c.c.) was heated for 2 hours with hydrazine sulphate (25·1 g.), also dissolved in N-sodium hydroxide (190 c.c.). On being cooled the mixture deposited a solid which, recrystallised from alcohol, formed needles, m. p. 157° (34 g., 96%). Oppenheim (*loc. cit.*) records m. p. 157·5°.

6-Phenyl-4-methyl-3-pyridazone.—The pyridazinone (26·5 g.) was dissolved in hot glacial acetic acid (75 c.c.), and bromine (22 g.) added dropwise. Hydrogen bromide was evolved. After addition of all the bromine, the solution was heated at 100° for 15 minutes, then cooled, and poured into ice–water (400 c.c.), whereupon a white solid separated. This, after being kept overnight, was filtered off and recrystallised from dilute alcohol, forming plates, m. p. 189° (22 g., 83%). It was identical with the 6-phenyl-4-methyl-3-pyridazone obtained by condensation of β-benzoyl-α-methylacrylic acid with hydrazine.

β-Benzoylacrylic Acid.—This was prepared according to the following modification of the method of von Pechmann (*Ber.*, 1882, **15**, 883). Maleic anhydride (20 g.) was dissolved in dry benzene (200 c.c.) and treated with finely ground anhydrous aluminium chloride (30 g.), and the mixture heated at 60° for 3 hours. The excess of aluminium chloride was then decomposed with dilute hydrochloric acid, and the solution extracted with benzene. The dried ($MgSO_4$) extract was evaporated and the residue recrystallised from water; β-benzoylacrylic acid formed plates, m. p. 64°; yield, 27 g. (75%).

The authors are grateful to the Colonial Products Research Council for their support and to Messrs. Kemball-Bishop and Co. Ltd. for a generous gift of itaconic acid.

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455. *Properties and Orientation of Some Derivatives of 3-Acylchromones.*

By WILSON BAKER and V. S. BUTT.

3-Acylchromones are produced by acylation of either *o*-hydroxyacetophenones or *o*-hydroxy-1 : 3-diketones of the type (IV). In the general case the product may possess either of the alternative structures (VI) or (VII), and there has hitherto been no satisfactory method for distinguishing between such isomerides, as the only procedure, that of degradative hydrolysis to an unacylated chromone, here reviewed, is usually ambiguous. A method for distinguishing between these isomerides has now been found in their reaction with benzylamine, which splits off the 3-acyl group as an acylbenzylamine and reacts with the rest of the molecule to give a yellow, fluorescent derivative of the type (XI).

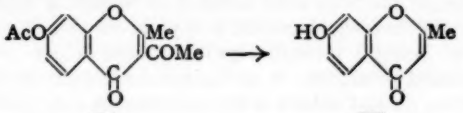
The reaction between 3-acylchromones and phenylhydrazine has been shown to yield 4-acyl-1-phenyl-5-*o*-hydroxyphenyl-3-alkylpyrazoles of the type (XXI).

THE reaction of *o*-hydroxyacetophenones, or their substituted derivatives, with the anhydride and the sodium salt of an aliphatic or aromatic carboxylic acid has been widely used for the preparation of chromones, including many flavones and flavonols. In certain cases where an acid of the type $CH_2R{\cdot}CO_2H$ is used coumarins have also been obtained, and whether a chromone or coumarin or a mixture of both is produced depends on the structures of the acid and of the ketone used and on the reaction conditions employed (see, for example, Sethna and Shah, *Chem. Reviews*, 1945, **36**, 8).

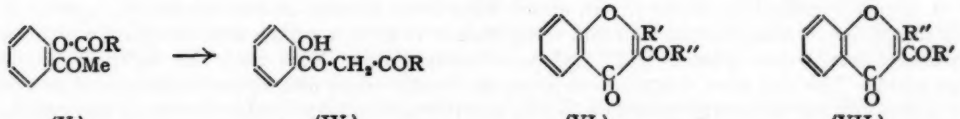
A 3-acylchromone is another type of product which may be formed in this reaction; this was first established by von Kostanecki *et al.* (*Ber.*, 1901, **34**, 102, 2946) in the case of 7-acetoxy-3-acetyl-2-methylchromone (I) prepared from resacetophenone, acetic anhydride, and sodium acetate.

Other cases of the similar formation of 3-acylchromones have since been recorded, and it was shown by Baker (*J.*, 1933, 1383) that the production of these compounds is a general feature of the reaction, but that owing to the fact that the whole reaction product was usually subjected to

vigorous alkaline hydrolysis the 3-acyl group was lost and a chromone unsubstituted in position 3, for example (II), was isolated.



(I.) (II). (III.)



(V.) (IV.) (VI.) (VII.)

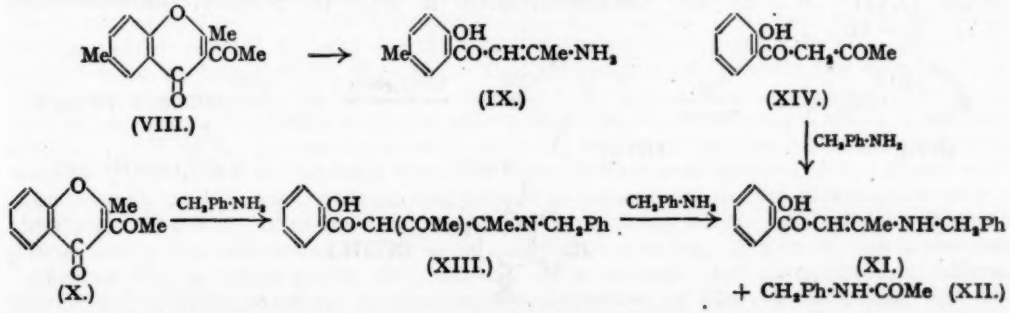
3-Acylchromones can also be similarly prepared from 1 : 3-diketones of the type (IV), and it was first established by Baker (*loc. cit.*; see also Mahal and Venkataraman, *Current Science*, 1933, **2**, 214) that these diketones were formed in the reaction under discussion by intramolecular migration of the acyl group R·CO from the phenolic oxygen atom in the *o*-acyloxyacetophenone (V). It was also shown that the same chromone was produced both from 2-propionoacetyl-4-methylphenol, acetic anhydride, and sodium acetate, and from 2-acetoacetyl-4-methylphenol, propionic anhydride, and sodium propionate, so that the reaction clearly involves the formation of an intermediate triacylmethane of the type (III). In the more general case of 3-acylchromones prepared from preformed 1 : 3-diketones of the type (IV) and the anhydride and sodium salt of an acid R″·CO_2H (Müller, *J.*, 1915, **107**, 872; Wittig, Bangert, and Richter, *Annalen*, 1925, **446**, 155; Algar, McCarthy, and Dick, *Proc. Roy. Irish Acad.*, 1933, **41**, 155; Baker, *loc. cit.*) the product might therefore possess either of the isomeric structures (VI) or (VII).

Hydrolytic evidence hitherto employed to establish the structure of these 3-acylchromones has been criticised (Baker, *loc. cit.*) on the grounds that the nature of the product will depend on whether the 3-acyl group is removed by direct hydrolysis, or whether the heterocyclic ring is first opened to give a triacylmethane of the type (III), which then loses one acyl group by hydrolysis and subsequently undergoes ring-closure.

The main object of the present investigation has been to devise methods which could be used to distinguish between isomeric 3-acylchromones of the types (VI) and (VII), without recourse to alkaline hydrolysis. This is also a problem of interest in connection with the structure of buddleoflavonol, a yellow colouring matter occurring as a glycoside in *Buddleia variabilis*, Hemsl., which according to Yü (*Bull. Soc. Chim. biol.*, 1933, **15**, 482) is 5 : 7-dihydroxy-4′-methoxy-3-acetylflavone, but which might on the available evidence be the isomeric 5 : 7-dihydroxy-3-anisoyl-2-methylchromone.

Reaction of 3-Acylchromones with Amines or Ammonia.

The reaction between 3-acylchromones and alcoholic ammonia was investigated by Schneider and Kunau (*Ber.*, 1921, **54**, 2304), Schneider and Bode (*Ber.*, 1923, **56**, 1042), Wittig (*Ber.*, 1925, **58**, 19), and Wittig and Blumenthal (*Ber.*, 1927, **60**, 1085). Wittig and Blumenthal showed that with 3-acetyl-2 : 6-dimethylchromone (VIII) loss of an acetyl group and addition of ammonia occurred to give 2-β-aminocrotonyl-4-methylphenol (IX), which was also produced by the



(VIII.) (IX.) (XIV.)

(X.) (XIII.) (XI.)

+ $CH_2Ph·NH·COMe$ (XII.)

action of alcoholic ammonia on 2-acetoacetyl-4-methylphenol or on 2 : 6-dimethylchromone. It was suggested that this compound was produced by fission of the acetyl group in (VIII)

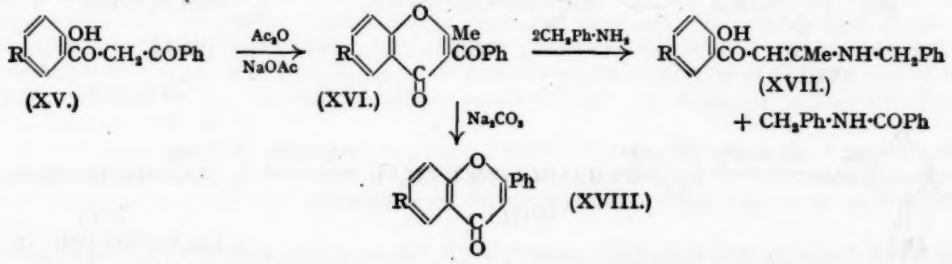
followed by hydrolytic opening of the chromone ring and reaction of ammonia with the resulting 1 : 3-diketone.

In the present investigation benzylamine has been used in place of ammonia, and it has been shown that the method serves to distinguish between isomeric 3-acylchromones of the types (VI) and (VII). Benzylamine was chosen as being a powerful primary base which readily reacts with 3-acylchromones to give easily isolated products; a secondary base such as diethylamine and weaker bases, for example, *p*-toluidine do not attack 3-acylchromones even under vigorous conditions.

3-Acetyl-2-methylchromone (X) in either anhydrous alcohol or benzene reacts rapidly with two molecules of benzylamine at room temperature to give a yellow solution from which both 2-β-*benzylaminocrotonylphenol* (XI) and acetobenzylamide (XII) may be isolated in very high yield. The fact that this reaction proceeds rapidly under anhydrous conditions shows that the hydrolytic mechanism proposed by Wittig and Blumenthal is probably incorrect, and certainly cannot apply to the reactions now recorded. We regard the reaction as initiated by the attack of the anionoid benzylamine on the carbon atom in position 2 which is strongly cationoid owing to conjugation with the two carbonyl groups, and the resulting product, in which benzylamine is added to the double bond between carbon atoms 2 and 3, would then be expected to rearrange to the more stable open-chain Schiff's base (XIII) (for work on the addition of amines to αβ-unsaturated carbonyl compounds see Tambor and Wildi, *Ber.*, 1898, **31**, 349; Ruhemann, *J.*, 1903, **83**, 1371; 1904, **85**, 1451; Ruhemann and Watson, *J.*, 1904, **85**, 456, 1170). This Schiff's base (XIII), in which carbon atom 2 of the chromone nucleus with its attached methyl group is labelled by the benzylimino-group, would be expected to behave like a triacylmethane since the >C=N⁻ group is analogous to a carbonyl group. Claisen showed that triacylmethanes readily lose an acyl group as an acid amide when reacted upon with a base (*Annalen*, 1893, **277**, 204; 1896, **291**, 99), and the further reaction of (XIII) with benzylamine would, therefore, be expected to yield the observed products, namely 2-β-benzylaminocrotonylphenol (XI) and acetobenzylamide (XII). Loss of the 3-acetyl group as acetobenzylamide cannot precede the opening of the heterocyclic ring, because 2-methylchromone is attacked by benzylamine to give (XI) much more slowly than is the 3-acyl derivative. Compound (XI) is also very readily prepared from 2-acetoacetylphenol (XIV) and benzylamine. It may be noted that reaction of a secondary amine with a 3-acylchromone could not give rise to a Schiff's base of the type (XIII), thus accounting for the failure of the reaction in these cases.

Reaction with benzylamine, therefore, serves to distinguish between the isomerides of the general types (VI) and (VII), the former giving *o*-HO·C_6H_4·CO·CH:CR′·NH·CH_2Ph and the amide CH_2Ph·NH·COR″, and the latter giving *o*-HO·C_6H_4·CO·CH:CR″·NH·CH_2Ph and the amide CH_2Ph·NH·COR′. Several other cases of the reaction have been carried out, including some with 3-acylchromones having different groups R′ and R″, the structures of which have not hitherto been established.

7-Methoxy-3-acetyl-2-methylchromone reacts with benzylamine to give *5-methoxy-2-β-benzylaminocrotonylphenol* and acetobenzylamide. Müller (*J.*, 1915, **107**, 872) prepared *o*-hydroxydibenzoylmethane (XV; R = H) by the partial hydrolysis of flavone, and by heating this compound with acetic anhydride and anhydrous sodium acetate obtained an "acetyl derivative" (actually an anhydroacetyl derivative) for which no structure was proposed and which might be either 3-benzoyl-2-methylchromone (XVI; R = H) or 3-acetylflavone (see Baker, *loc. cit.*). Since, however, it reacts with benzylamine to give 2-β-benzylaminocrotonylphenol (XVII; R = H) and benzobenzylamide it must be *3-benzoyl-2-methylchromone* (XVI; R = H).



(XV.) (XVI.) (XVII.) + CH_2Ph·NH·COPh (XVIII.)

A similar case is provided by the compound prepared by Wittig and Blumenthal (*Ber.*, 1927, **60**, 1085) by heating the *O*-benzoyl derivative of 2-β-aminocrotonyl-4-methylphenol; this was

regarded as 3-acetyl-6-methylflavone because it could be hydrolysed to 6-methylflavone. The compound, however, reacts with benzylamine to give 2-β-*benzylaminocrotonyl-4-methylphenol* (XVII; R = Me), and must, therefore, be 3-*benzoyl*-2 : 6-*dimethylchromone* (XVI; R = Me), a conclusion which brings to light an interesting migration of the benzoyl group from oxygen to carbon when the *O*-benzoyl derivative of 2-β-aminocrotonyl-4-methylphenol is heated. The benzylamino-compound (XVII; R = Me) was also prepared from benzylamine and 2-acetoactyl-4-methylphenol.

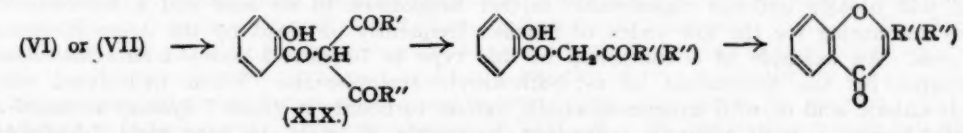
3-Propionyl-2 : 6-dimethylchromone reacted with benzylamine to give (XVII; R = Me) with loss of the propionyl group, thus definitely establishing the structure of this chromone which had been previously suggested on the basis of its hydrolysis to 2 : 6-dimethylchromone (Wittig, Bangert, and Richter, *loc. cit.*; see, however, Baker, *loc. cit.*, and below). The preparation of this chromone is mentioned on p. 2143.

Two derivatives of a 7-acyloxychromone which have been examined react differently with benzylamine. 7-Acetoxy-3-acetyl-2-methylchromone reacts in cold benzene solution to give merely 7-hydroxy-3-acetyl-2-methylchromone, thus showing that the 7-hydroxy-group stabilises the heterocyclic ring (see section Hydrolysis of 3-Acylchromones, below), and confirming that in the cases of the chromones previously discussed the loss of the 3-acyl substituent occurs after the opening of the ring. In the case of 7-benzoyloxy-3-benzoylflavone reaction at room temperature with benzylamine in benzene gave an uncrystallisable mixture

The unsaturated benzylamine derivatives, as (XI) and (XVII) described above, are represented as " enamines " rather than " ketimines," since the former conjugated structure is more consistent with their bright yellow-green colour, and with the fact that they exhibit vivid yellow-green fluorescences in ultra-violet light. The benzyl group is not essential for colour or fluorescence; 2-β-*methylaminocrotonylphenol*, prepared from 2-acetoacetylphenol and 2-β-aminocrotonyl-4-methylphenol (Wittig and Blumenthal, *loc. cit.*), also exhibits these characteristics.

Hydrolysis of 3-Acylchromones.

Chromones and flavones have frequently been prepared by the partial hydrolysis of their 3-acyl derivatives [see, for example, the preparation of the chromone (II) from the 3-acetylchromone (I)], and it has been generally assumed that the reaction involves direct hydrolytic fission of the 3-acyl group. On this assumption Wittig, Bangert, and Richter (*loc. cit.*) have allotted structures to chromones of the type (VI) and (VII) where R′ and R″ represent different groups, but it was pointed out by Baker (*loc. cit.*) that this evidence of structure is inconclusive in any case where the reaction may involve ring opening to give the triacylmethane (XIX), because the particular acyl group lost and the structure of the final product would depend solely on the nature of the groups R′ and R″ and not on their position in the original chromone.



Direct evidence of the formation of triacylmethanes during hydrolysis of certain 3-acylchromones (orientation determined by reaction with benzylamine) has now been obtained. 3-Benzoyl-2-methylchromone (XVI; R = H) undergoes hydrolysis with aqueous-alcoholic sodium carbonate to give flavone (XVIII; R = H) and not 2-methylchromone which would have been produced by direct loss of the 3-benzoyl group. A similar case is provided by the hydrolysis (Wittig and Blumenthal, *loc. cit.*) of 3-benzoyl-2 : 6-dimethylchromone (XVI; R = Me) which yields 6-methylflavone (XVIII; R = Me). That the chromone ring should first open and then close under the same reaction conditions receives a natural explanation as follows. The ready opening of the ring is initiated by attack of hydroxyl ions at carbon atom 2, which is rendered strongly cationoid by the two carbonyl groups (cf. the rapid reaction of benzylamine with 3-acylchromones), and the resulting triacylmethane (XIX) is then hydrolysed to a 2-acetoacylphenol which does, in fact, undergo ring closure in presence of sodium carbonate to give a chromone. The latter point has been established by cyclising *o*-hydroxydibenzoylmethane to flavone under the influence of boiling sodium carbonate solution; it may be mentioned that cyclisation also occurs in boiling 50% alcohol. It is probable that an equilibrium between flavone and diketone is set up in solution, the proportion of diketone increasing with the alkalinity of the solution. As is well known, the action of caustic alkalis brings about further degradation of the 1 : 3-diketone, frequently in both possible ways.

The direction of hydrolysis of the intermediate triacylmethanes can be predicted from the work of Claisen (*Annalen*, 1893, **277**, 192), who showed that such compounds containing two aroyl groups and one aliphatic acid residue are hydrolysed with loss of the aliphatic group. The direction of hydrolysis is less certain when the chromone can yield a triacylmethane containing two different aliphatic residues, and the reaction is further complicated in these cases by the possibility that the aliphatic 3-acyl group of the chromone may undergo direct hydrolytic fission. Thus the hydrolysis of 3-propionyl-2 : 6-dimethylchromone with aqueous-alcoholic sodium carbonate (Wittig, Bangert, and Richter, *loc. cit.*; Baker, *loc. cit.*) gave a poor yield of 2 : 6-dimethylchromone as the sole neutral product, and the absence of 6-methyl-2-ethylchromone strongly suggests that two simultaneous reactions are occurring, (*a*) direct fission of the 3-propionyl group to give the relatively stable 2 : 6-dimethylchromone, and (*b*) ring opening to the triketone which breaks down to the two diketones by partial loss of both acetyl and propionyl groups, and subsequent further hydrolytic degradation of the two diketones rather than ring closure. Relevant observations are that 2-acetoacetyl-4-methylphenol is not cyclised under the above reaction conditions, and that 3-propionyl-2 : 6-dimethylchromone is hydrolysed by strong aqueous potassium hydroxide to give a mixture of volatile ketones in which methyl ethyl ketone has been identified as its 2 : 4-dinitrophenylhydrazone, m. p. 110°.

In these cases hydrolysis experiments are clearly insufficient to establish with certainty the structure of the parent chromone.

Hydrolysis of hydroxylated 3-acylchromones. 7-Hydroxy- and 5 : 7-dihydroxy-chromones and -flavones are very resistant towards alkaline hydrolysis, and this is probably due to the presence of neutralised systems between the hydroxyl groups and the carbonyl group in position 4, so that the latter cannot cause marked cationoid activity at carbon atom 2. This suggestion is supported by the fact that whilst flavone and 2-ethylchromone form 2 : 4-dinitrophenylhydrazones (Adkins and Mozingo, *J. Amer. Chem. Soc.*, 1938, **60**, 669), 7-hydroxyflavone does not react under the same conditions. With such hydroxylated chromones possessing an aliphatic 3-acyl group it therefore seems probable that when boiled with aqueous-alcoholic sodium carbonate, direct loss of the 3-acyl group occurs without opening of the pyrone ring, so that the structure of the chromone may be deduced from the nature of the products of hydrolysis (for examples see Kostanecki and Rozycki, *Ber.*, 1901, **34**, 102; Nagai, *Ber.*, 1892, **25**, 1284; Limaye and Kelkar, *Rasayanam*, 1936, **1**, 24; Gulati, Seth, and Venkataraman, *J.*, 1934, 1765).

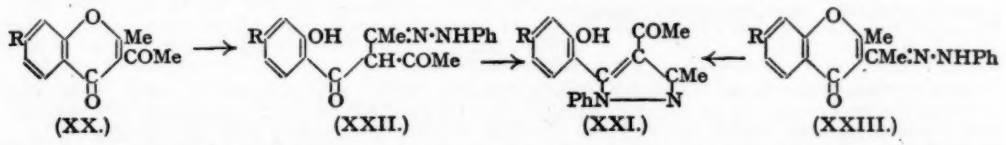
When, however, the 3-acyl substituent is an aroyl group, the hydroxylated derivatives are usually only attacked by alcoholic potassium hydroxide and, under these conditions, it is probable that the pyrone ring opens at least to a certain extent, so that the final product obtained after acidification may not be directly related to the original molecule. Moreover, the intermediate 1 : 3-diketone cannot cyclise under the strongly alkaline conditions of the hydrolysis, and will usually undergo considerable further breakdown to an acid and a monoketone, thus accounting for the low yields of flavones frequently obtained by the Allan–Robinson process. An example of a compound of this type is *7-acetoxy-3-benzoyl-2-methylchromone*, prepared by the acetylation of ω : 4-dibenzoylresacetophenone. When hydrolysed with hydrochloric acid or with aqueous-alcoholic sodium carbonate it yields *7-hydroxy-3-benzoyl-2-methylchromone*; with alcoholic potassium hydroxide it gives in poor yield 7-hydroxy-2-methylchromone and 2 : 4-*dihydroxydibenzoylmethane*. The structure assigned to the 3-acylchromone is based on (1) the stability of the 3-acyl group towards sodium carbonate, which suggests a benzoyl, rather than an acetyl group; (2) the production of 7-hydroxy-2-methylchromone, probably by direct hydrolytic fission of the benzoyl group, since if a triacylmethane were first produced by opening of the pyrone ring the acetyl and not the benzoyl group would be lost by hydrolysis, so that if subsequent ring closure occurred the product would be 7-hydroxyflavone; (3) analogy with the structure of 3-benzoyl-2-methylchromone which is prepared by a precisely similar reaction.

Reaction between 3-Acylchromones and Phenylhydrazine.

Tahara (*Ber.*, 1892, **25**, 1292) has described the reaction between phenylhydrazine and 7-methoxy-3-acetyl-2-methylchromone (XX; R = MeO) and the hydrolysis of the compound produced, but his results were interpreted on the basis of an erroneous naphthalene structure for the chromone (the correct formula was established by Kostanecki *et al.*, *Ber.*, 1901, **34**, 102, 2946), and no later investigation has been made. Without evidence, however, the primary product is formulated in the 4th Edition of Beilstein's "Handbuch der organischen Chemie," 1934, **18**, 108, as the simple phenylhydrazone of the carbonyl group in position 4.

Reinvestigation of the reaction between phenylhydrazine and some 3-acylchromones has been made.

3-Acetyl-2-methylchromone (XX; R = H) reacted with phenylhydrazine in alcoholic solution giving not a simple phenylhydrazone but a phenolic isomeride stable to alkalis. The compound is proved to be *4-acetyl-1-phenyl-5-o-hydroxyphenyl-3-methylpyrazole* (XXI; R = H) as follows. It exhibited normal phenolic properties, and gave a *methyl ether* by treatment with methyl sulphate and alkali. The presence of a *C*-acetyl group was established by a positive iodoform reaction, and by the formation of a 2 : 4-*dinitrophenylhydrazone* and a piperonylidene derivative. After reduction with sodium and alcohol it gave a purple colour with sulphuric acid and ferric chloride (Knorr pyrazoline reaction; *Ber.*, 1893, **26**, 101; 1909, **42**, 4411).



(XX.) (XXII.) (XXI.) (XXIII.)

In the formation of the pyrazole, the initial reaction is probably not between the phenylhydrazine and the 4-carbonyl group of the chromone (XX; R = H) which would lead to an isomeride of (XXI; R = H) having the phenyl group attached to the other nitrogen atom, because the 4-carbonyl group of the simple chromones is generally inert towards the usual ketonic reagents (see, for example, Simonis, *Samm. Chem. Vort.*, 1917, **24**, 438), although a few oximes (Wittig and Bangert, *Ber.*, 1925, **58**, 2627, 2636) and 2 : 4-dinitrophenylhydrazones (Adkins and Mozingo, *loc. cit.*) have been prepared, while the more likely condensation of phenylhydrazine with the 3-acetyl group would appear to be excluded by the fact that this phenylhydrazone (preparation described below) is very stable. The most probable first step, therefore, appears to be attack by the phenylhydrazine at carbon atom 2 (cf. the benzylamine reaction) to give a phenylhydrazone (XXII; R = H) of the open chain triacylmethane.

In acetic acid solution 3-acetyl-2-methylchromone (XX; R = H) gave a simple non-phenolic phenylhydrazone which, for the reasons given above, is assumed to be *2-methyl-3-(1-phenylhydrazonoethyl)chromone* (XXIII; R = H). By treatment with alcoholic potassium hydroxide, or better, aqueous alcoholic sodium carbonate, this phenylhydrazone underwent an isomeric change giving the same pyrazole (XXI; R = H) as had been previously prepared by the action of phenylhydrazine upon (XX; R = H) in alcoholic solution.

7-Methoxy-3-acetyl-2-methylchromone (XX; R = MeO) did not react smoothly with phenylhydrazine in alcoholic solution, but in acetic acid it gave a product agreeing in its properties with that prepared by Tahara under the same conditions. This compound, for the reasons given above, is regarded as 7-methoxy-2-methyl-3-(1-phenylhydrazonoethyl)chromone (XXIII; R = MeO). Treatment with alcoholic potassium hydroxide gave a product agreeing in most of its properties with the substance similarly prepared by Tahara, but this worker concluded, on the grounds of a nitrogen analysis only, that an acetyl group was lost during the course of the reaction. We now find that, as in the case of the phenylhydrazone (XXIII; R = H), the treatment with potassium hydroxide gives a phenolic isomeride which is now formulated as 4-acetyl-1-phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazole (XXI; R = MeO). The compound was characterised by the preparation of a 2 : 4-*dinitrophenylhydrazone*, an *acetyl* derivative, and a *monomethyl ether*.

The different reactions occurring between phenylhydrazine and 3-acylchromones in alcoholic and acetic acid solution find a parallel in the work of Auwers and Mauss (*Ber.*, 1926, **59**, 611) on the reaction between phenylhydrazine and ethyl benzylideneacetoacetate, which in alcohol gave an addition product at the olefinic bond, but which in acetic acid reacted to give the phenylhydrazone.

A few other pyrazole derivatives have been prepared during the course of this work. Interaction of phenylhydrazine with 2-acetoacetylphenol and with 5-methoxy-2-acetoacetylphenol gave *1-phenyl-5-o-hydroxyphenyl-3-methylpyrazole* and *1-phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazole* respectively. In these cases the location of the phenyl group at position 1 rather than position 2 is assumed by analogy with the structure of the pyrazole prepared by the action of phenylhydrazine upon benzoylacetone which has been proved to be 1 : 5-diphenyl-3-methylpyrazole (see Knorr, *Ber.*, 1887, **20**, 1096; Knorr and Duden, *ibid.*, 1893, **26**, 111; Auwers and Mauss, *loc. cit.*; Drumm, *Proc. Roy. Irish Acad.*, 1931, **40**, 106). Like the 4-acylpyrazoles previously described these pyrazoles give no ferric chloride reaction, but are soluble in dilute sodium hydroxide.

Reaction of phenylhydrazine with 2-hydroxy-4-methoxystyryl methyl ketone in alcohol gave directly what is probably 1-*phenyl*-5-(2-*hydroxy*-4-*methoxyphenyl*)-3-*methylpyrazoline* (cf. direct preparation of similar pyrazolines by Auwers and Voss, *Ber.*, 1909, **42**, 4411) since it give the Knorr pyrazoline test. The location of the phenyl group rests upon the likely assumption that the phenylhydrazine first reacts with the ketonic carbonyl group, rather than the olefinic bond.

7-*Methoxy*-2-*methyl*-4-*thionchromone* was prepared from 7-methoxy-2-methylchromone by the action of phosphorus pentasulphide. It reacted with alcoholic phenylhydrazine in presence of a trace of alkali to give 1-phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazole, identical with that previously prepared from phenylhydrazine and 5-methoxy-2-acetoacetylphenol. This observation is in contrast with those of Simonis and Rosenberg (*Ber.*, 1914, **47**, 1232) who have described the preparation of a number of phenylhydrazones of chromones by the reaction between phenylhydrazine and 4-thionchromones.

Experimental.

3-*Acetyl*-2-*methylchromone* (X).—2-Acetoacetylphenol (XIV) was prepared in 60% yield from *o*-hydroxyacetophenone (50 g.) (Wittig, Bangert, and Richter, *loc. cit.*; cf. preparation of 2-propionoacetyl-4-methylphenol, Baker, *loc. cit.*) and obtained as colourless needles from light petroleum (b. p. 60—80°), m. p. 101° (lit. m. p. 90·5—91·5°) (Found: C, 67·2; H, 5·4. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·6%); this compound was then converted into 3-acetyl-2-methylchromone, m. p. 89°, by treatment with acetic anhydride and anhydrous sodium acetate. The 2 : 4-*dinitrophenylhydrazone* of 3-acetyl-2-methylchromone, prepared by the use of Brady's reagent (*J.*, 1931, 757), separated from acetic acid as orange-yellow needles, m. p. 252° (Found: C, 57·3; H, 3·9. $C_{18}H_{14}O_6N_4$ requires C, 56·6; H, 3·7%).

2-β-*Benzylaminocrotonylphenol* (XI).—(a) *From* 2-*acetoacetylphenol*. To the diketone (0·5 g.) in alcohol (10 c.c.) was added benzylamine (0·3 g.), and after 1 hour the yellow solution when disturbed began to deposit crystals. After 24 hours the yellow-green needles (0·45 g.) of 2-β-*benzylaminocrotonylphenol* (XI) were collected; these had m. p. 124° both before and after crystallisation from alcohol (Found: C, 76·4; H, 6·4; N, 5·2. $C_{17}H_{17}O_2N$ requires C, 75·9; H, 6·3; N, 5·4%). The compound is insoluble in aqueous sodium hydroxide, gives an intense greenish-brown coloration with alcoholic ferric chloride, and shows a vivid yellow-green fluorescence in ultra-violet light. The compound is sparingly soluble in alcohol but readily soluble in benzene, and is dimorphous. It separates from light petroleum (b. p. 60—80°) or usually from alcohol in the form of long needles, but may also separate, sometines simultaneously, in the form of thick, almost rectangular tablets, both forms appearing to melt at the same temperature. The tablet form is frequently obtained by slow crystallisation from alcohol.

(b) *From* 3-*acetyl*-2-*methylchromone* (X). Benzylamine (2·2 g., 2 mols.) was added to the chromone (2 g., 1 mol.) dissolved in benzene (10 c.c.), and the bright yellow solution was left at room temperature for 24 hours and the solvent then removed under diminished pressure on the water-bath. The yellow, crystalline solid was crushed, shaken for 10 minutes with warm water (30 c.c.), filtered, washed with warm water and dried, giving 2-β-benzylaminocrotonylphenol (XI) as a bright yellow powder (2·5 g.; theory requires 2·7 g.), m. p. 122—123°. Crystallisation from ethyl alcohol readily gave the pure compound, m. p. 124° (2·4 g.). The aqueous filtrate and washings were evaporated to dryness giving directly acetobenzylamide (1·5 g.; theory requires 1·5 g.), m. p. 53—55°; recrystallisation from carbon tetrachloride–light petroleum (b. p. 60—80°) gave the pure compound, m. p. and mixed m. p. with an authentic specimen 62°.

When a similar reaction was carried out in alcohol (40 c.c.) the yellow solution began to deposit crystals of (XI) after 3 hours; these could be collected in the pure state, but the yield was somewhat less than that obtained in benzene solution.

(c) *From* 2-*methylchromone*. A mixture of the chromone (0·5 g.) and benzylamine (0·35 g.) in alcohol (5 c.c.) reacted slowly at room temperature depositing crystals after 2 days. The golden-yellow plates (0·6 g.) of (XI) which had separated after 9 days had m. p. and mixed m. p. 124°. Recrystallisation from alcohol under normal conditions gave the usual needle form, reconverted into the plate form by very slow crystallisation. The same reaction mixture when heated under reflux for 3 hours and then cooled gave (XI) (0·35 g.).

(d) *From* 3-*benzoyl*-2-*methylchromone* (XVI; R = H) *o*-Hydroxydibenzoylmethane, prepared by molecular rearrangement of *o*-benzoyloxyacetophenone (Baker, *loc. cit.*) was converted into 3-benzoyl-2-methylchromone (Müller, *loc. cit.*). The chromone (0·2 g.), alcohol (3 c.c.), and benzylamine (0·2 g.) were heated under reflux for 3 hours, yielding yellow-green needles of 2-β-benzylaminocrotonylphenol, m. p. and mixed m. p. 123°–124°. Evaporation of the mother-liquors and crystallisation of the residue from light petroleum (b. p. 60—80°) gave benzobenzylamide, m. p. and mixed m. p. with a genuine specimen (Dermer and King, *J. Org. Chem.*, 1943, **8**, 169) 106—107°.

7-*Methoxy*-2-*methylchromone and* 7-*Methoxy*-3-*acetyl*-2-*methylchromone*.—Paeonol (2-hydroxy-4-methoxyacetophenone) was converted into 5-methoxy-2-acetoacetylphenol (cf. previous preparation) which formed fine needles, m. p. 71—72° from benzene–light petroleum (b. p. 40—60°; 2 : 1) (Nagai, *loc. cit.*, gives m. p. 68°) (Found: C, 63·4; H, 5·8. Calc. for $C_{11}H_{12}O_4$: C, 63·5; H, 5·8%), and thence by solution in hot 10% hydrochloric acid into 7-methoxy-2-methylchromone, m. p. 115° (Found: C, 69·6; H, 5·4. Calc. for $C_{11}H_{10}O_3$: C, 69·5; H, 5·3%). Treatment of the diketone with acetic anhydride and anhydrous sodium acetate at 160—180° for 3 minutes gave 7-methoxy-3-acetyl-2-methylchromone as colourless needles, m. p. 162° (from alcohol), which became yellow on exposure to light (Found: C, 67·4; H, 5·3. Calc. for $C_{13}H_{12}O_4$: C, 67·2; H, 5·2%); the 2 : 4-*dinitrophenylhydrazone* separated from glacial acetic acid as orange plates, m. p. 262° (decomp.) (Found: C, 56·0; H, 3·4. $C_{19}H_{16}O_7N_4$ requires C, 55·3; H, 3·9%).

5-*Methoxy*-2-β-*benzylaminocrotonylphenol*.—7-Methoxy-3-acetyl-2-methylchromone (1 g.), anhydrous

alcohol (20 c.c.), and benzylamine (0·9 g.) were heated under reflux for 7 hours, and after cooling the crystalline material (1·1 g.) was collected and recrystallised from ethyl alcohol. The *5-methoxy-2-β-benzylaminocrotonylphenol* formed very pale yellow-green needles, m. p. 136° (Found: C, 72·4; H, 6·5; N, 5·0. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%). The crystals become yellow on prolonged exposure to light, show a blue-green fluorescence in ultra-violet light, and give an intense dull olive-green coloration with alcoholic ferric chloride. The mother-liquors from the reaction mixture yielded acetobenzylamide as needles from light petroleum (b. p. 60—80°), m. p. and mixed m. p. 62—63°.

2-β-Benzylaminocrotonyl-4-methylphenol (XVII; R = Me).—(a) *From 2-acetoacetyl-4-methylphenol.* 2-Acetoacetyl-4-methylphenol (1 g.), alcohol (10 c.c.), and benzylamine (0·5 g.) were heated under reflux for 7 hours, giving *2-β-benzylaminocrotonyl-4-methylphenol* (0·75 g.) as yellow-green, diamond-shaped plates from alcohol, m. p. 123° (Found: C, 77·0; H, 6·6; N, 5·0. $C_{18}H_{19}O_2N$ requires C, 76·9; H, 6·8; N, 5·0%). The substance shows a bright yellow-green fluorescence in ultra-violet light, and gives a dark olive-green coloration with alcoholic ferric chloride.

(b) *From 3-benzoyl-2 : 6-dimethylchromone.* The chromone (0·28 g.), alcohol (4 c.c.), and benzylamine (0·21 g.) were heated under reflux for 1 hour, and from the resulting solution was isolated 2-β-benzylaminocrotonyl-4-methylphenol (0·075 g.), m. p. 122—123°.

(c) *From 3-propionyl-2 : 6-dimethylchromone.* The chromone (0·2 g.), alcohol (5 c.c.), and benzylamine (0·2 g.) were heated under reflux for 3 hours and yielded the characteristic plates of 2-β-benzylaminocrotonyl-4-methylphenol, m. p. and mixed m. p. 122—123°.

2-β-Methylaminocrotonylphenol.—To a solution of 2-acetoacetylphenol (0·5 g.) in alcohol (5 c.c.) was added a 30% solution of methylamine (0·3 c.c.), and the crystals (0·13 g.) which began to separate after 24 hours were collected after 3 days, and crystallised from light petroleum (b. p. 60—80°). *2-β-Methylaminocrotonylphenol* formed yellow-green, thick needles, m. p. 101° (Found: C, 68·7; H, 6·9; N, 7·9. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8; N, 7·3%). It exhibits a bright green fluorescence in ultra-violet light.

Hydrolysis of 3-Benzoyl-2-methylchromone (XVI; R = H).—The chromone (0·1 g.) in alcohol (5 c.c.) was heated under reflux for ½ hour with 2N-sodium carbonate (5 c.c.), water added, kept at 0°, and the crystalline product (0·03 g.) collected. After crystallisation from light petroleum (b. p. 60—80°) it formed needles, m. p. and mixed m. p. with an authentic specimen of flavone 98°.

Ring Closure of o-Hydroxydibenzoylmethane.—(*a*) The diketone (0·1 g.) in alcohol (5 c.c.) was heated under reflux for ½ hour with 2N-sodium carbonate (5 c.c.), diluted, and kept at 0°. The colourless needles (0·04 g.) after crystallisation from light petroleum (b. p. 60—80°) melted at 97·5°, either alone or when mixed with flavone. (*b*) A similar experiment using water in place of the 2N-sodium carbonate, and heating the solution under reflux for 18 hours, gave unchanged diketone (0·03 g.) and flavone (0·05 g.).

7-Acetoxy-3-benzoyl-2-methylchromone.—ω : 4-Dibenzoylresacetophenone (Baker, *loc. cit.*) (5 g.), acetic anhydride (5 c.c.), and anhydrous sodium acetate (5 g.) were heated under reflux for ½ hour, poured into water, and extracted with ether, the ethereal solution was washed with excess of 2N-sodium carbonate, and dried, and the solvent evaporated. The residue was crystallised from light petroleum (b. p. 80—100°) giving colourless needles (1·7 g.) of *7-acetoxy-3-benzoyl-2-methylchromone*, m. p. 132° (Found: C, 70·4; H, 4·4. $C_{19}H_{14}O_5$ requires C, 70·8; H, 4·4%). The 2 : 4-*dinitrophenylhydrazone* separated from aqueous dioxan as orange needles, m. p. 295—197° (decomp.) (Found: C, 60·0; H, 3·7. $C_{25}H_{18}O_8N_4$ requires C, 59·8; H, 3·6%).

Hydrolysis of 7-Acetoxy-3-benzoyl-2-methylchromone.—(*a*) Heating with concentrated hydrochloric acid for 5 minutes, or with aqueous-alcoholic sodium carbonate for ½ hour, gave *7-hydroxy-3-benzoyl-2-methylchromone* as needles, m. p. 243°, from alcohol (Found: C, 72·9; H, 4·3. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%). (*b*) Hydrolysis of the chromone (0·5 g.) in alcohol (20 c.c.) with potassium hydroxide (0·5 g.) in water (0·5 c.c.) for 20 minutes, dilution, and saturation with carbon dioxide gave a yellow solid which was extracted with light petroleum (b. p. 60—80°) in a Soxhlet apparatus for 6 hours, yielding 2 : 4-*dihydroxydibenzoylmethane* (0·06 g.) as pale yellow needles, m. p. 162°, from benzene (Found: C, 70·3; H, 4·6. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%). The petroleum-insoluble material was crystallised several times from dilute alcohol (charcoal) and proved to be 7-hydroxy-2-methylchromone, m. p. 249°. (*c*) Air was aspirated through solutions of the chromone (0·1 g.) in 20% aqueous potassium hydroxide at 100° and 2 : 4-dinitrophenylhydrazine in hydrochloric acid and the orange 2 : 4-dinitrophenylhydrazone of acetone (0·003 g.), m. p. 123°, was obtained during 2½ hours.

2 : 4-*Dinitrophenylhydrazones.*—*3-Propionyl-2 : 6-dimethylchromone* 2 : 4-*dinitrophenylhydrazone* separated from ethyl alcohol in yellow needles, m. p. 215° (decomp.) (Found: C, 58·0; H, 4·3. $C_{20}H_{16}O_8N_4$ requires C, 58·5; H, 4·4%). The 2 : 4-*dinitrophenylhydrazone* of 7-acetoxy-3-acetyl-2-methylchromone (Kostanecki and Rozycki, *Ber.*, 1901, **34**, 102) crystallised from alcohol–ethyl acetate (2 : 1) in pale yellow needles, m. p. 172° (Found: C, 54·4; H, 3·8. $C_{20}H_{16}O_8N_4$ requires C, 54·5; H, 3·6%).

Action of Phenylhydrazine on 3-Acetyl-2-methylchromone in Alcohol.—To 3-acetyl-2-methylchromone (XX; R = H) (10 g.), dissolved in warm alcohol (50 c.c.), was added phenylhydrazine (5 g.) and after 15 minutes the mixture was allowed to cool. The crystalline precipitate (7 g.) was collected, washed, and crystallised from pyridine–alcohol (1 : 4), giving *4-acetyl-1-phenyl-5-o-hydroxyphenyl-3-methylpyrazole* (XXI; R = H) as colourless, compact bi-pyramids, m. p. 237° (decomp.) (Found: C, 74·1; H, 5·6; N, 9·6. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%). It gives no ferric chloride reaction, but is soluble in cold sodium hydroxide solution, from which it may be recovered even after boiling for several hours. By treatment with 2N-sodium hydroxide and iodine–potassium iodide solution at 60° it gave iodoform, m. p. 119°; with piperonal (1 mol.) in aqueous-alcoholic sodium hydroxide it gave a piperonylidene derivative, m. p. 186—187°, and, after reduction with sodium and alcohol, it showed the Knorr pyrazoline reaction. The 2 : 4-*dinitrophenylhydrazone* formed dark red needles from acetic acid, m. p. 225° (Found: C, 61·5; H, 4·2; N, 18·3. $C_{24}H_{20}O_5N_6$ requires C, 61·0; H, 4·2; N, 17·8%). By shaking the pyrazole (1 g.) for 2 hours at room temperature with sodium hydroxide (3 g.) in water (10 c.c.) and methyl sulphate (0·75 g.) the *methyl ether* (0·3 g.) separated; by crystallisation from alcohol this formed thick needles, m. p. 133° (Found: C, 74·2; H, 5·9; N, 9·4. $C_{19}H_{18}O_2N_2$ requires C, 74·5; H, 5·9; N, 9·2%).

Action of Phenylhydrazine on 3-*Acetyl*-2-*methylchromone in Acetic Acid.*—Phenylhydrazine (5 g.) was added to 3-acetyl-2-methylchromone (XX; R = H) (10 g.) in glacial acetic acid (30 c.c.). The crystals 2·5 g.) which separated were collected after 24 hours and crystallised from acetic acid (charcoal) and then from dioxan, being obtained as rhombic tablets, m. p. 194—195° (Found: C, 74·0; H, 5·6; N, 9·4. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%). 2-*Methyl*-3-(1-*phenylhydrazonoethyl*)*chromone* (XXIII; R = H) shows no phenolic properties.

Treatment of 2-*Methyl*-3-(1-*phenylhydrazonoethyl*)*chromone with Alkali.*—The phenylhydrazone (XXIII; R = H) (1·5 g.) was heated under reflux with (*a*) alcohol (60 c.c.) and 2N-sodium carbonate (60 c.c.) for 6 hours, or (*b*) alcohol (15 c.c.) and potassium hydroxide (1·5 g.) in water (15 c.c.) for 1 hour, the solutions then evaporated, water added, and, in the second case, acidified. The precipitates (*ca.* 1·1 g.) were crystallised several times from alcohol (charcoal) giving the pyrazole (XXI; R = H), m. p. 243° (decomp.) (Found: C, 73·5; H, 5·6; N, 9·4. Calc. for $C_{18}H_{16}O_2N_2$: C, 74·0; H, 5·5; N, 9·6%). Complete identity with the previous specimen, which, owing to decomposition, is not satisfactorily established by mixed melting-point, was proved by mixed melting-point determinations of the related 2 : 4-dinitrophenylhydrazones and the methyl ethers.

Action of Phenylhydrazine on 7-*Methoxy*-3-*acetyl*-2-*methylchromone.*—Phenylhydrazine (1·5 g.) was added to a solution of 7-methoxy-3-acetyl-2-methylchromone (XX; R = MeO) (2·4 g.) in glacial acetic acid (50 c.c.) with cooling. Crystals soon separated and were later collected (1·7 g.) and recrystallised from acetic acid, giving colourless, prismatic needles of 7-methoxy-2-methyl-3-(1-phenylhydrazonoethyl)-chromone (XXIII; R = MeO), m. p. 210° (lit. 213°) (Found: C, 70·5; H, 5·7; N, 8·6. Calc. for $C_{19}H_{18}O_3N_2$: C, 70·8; H, 5·6; N, 8·7%), showing no phenolic properties.

4-*Acetyl*-1-*phenyl*-5-(2-*hydroxy*-4-*methoxyphenyl*)-3-*methylpyrazole* (XXI; R = MeO).—The phenylhydrazone (XXIII; R = MeO) (1 g.) in alcohol (20 c.c.) was heated under reflux with potassium hydroxide (1 g.) in water (5 c.c.) for 2 hours. The solution was concentrated, water was added, and the solution acidified, precipitating a solid (0·9 g.) which was crystallised from dilute alcohol (charcoal) and then from chloroform–light petroleum (b. p. 60—80°), giving 4-*acetyl*-1-*phenyl*-5-(2-*hydroxy*-4-*methoxyphenyl*)-3-*methylpyrazole* (XXI; R = MeO) as fine colourless needles, m. p. 206° (decomp.) (Found: C, 70·8; H, 5·6; N, 9·2. $C_{19}H_{18}O_3N_2$ requires C, 70·8; H, 5·6; N, 8·7%). This pyrazole gives no ferric chloride reaction when pure, but the crude material gave a red colour as described by Tahara. It is soluble in cold aqueous sodium hydroxide, and after reduction with sodium and alcohol gives the Knorr reaction for pyrazolines. The 2 : 4-*dinitrophenylhydrazone* forms fine, orange needles, m. p. 183°, from benzene (Found: C, 59·5; H, 3·8; N, 16·7. $C_{25}H_{22}O_6N_6$ requires C, 59·8; H, 4·4; N, 16·7%). The *acetyl* derivative (acetic anhydride and pyridine for 1½ hours at 100°, followed by addition of water) separated from alcohol in rectangular plates, m. p. 194° (Found: C, 68·6; H, 5·5; N, 7·6. $C_{21}H_{20}O_4N_2$ requires C, 69·2; H, 5·5; N, 7·7%). The methyl ether, prepared as in the case of the pyrazole (XXI; R = H), separated from dilute alcohol in colourless, prismatic needles, m. p. 150° (lit. 150°) (Found: C, 70·8; H, 5·7; N, 9·0. Calc. for $C_{20}H_{20}O_3N_2$: C, 71·4; H, 5·9; N, 8·3%).

1-*Phenyl*-5-o-*hydroxyphenyl*-3-*methylpyrazole.*—Phenylhydrazine (1 g.), 2-acetoacetylphenol (1·5 g.), and alcohol (20 c.c.) were heated under reflux for 1 hour, most of the alcohol was distilled off, and water added. The precipitated material crystallised from dilute alcohol in colourless needles, m. p. 190—191° (Found: C, 76·8; H, 6·0; N, 10·1. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%). 1-*Phenyl*-5-o-*hydroxyphenyl*-3-*methylpyrazole* is soluble in dilute sodium hydroxide but gives no coloration with alcoholic ferric chloride.

1-*Phenyl*-5-(2-*hydroxy*-4-*methoxyphenyl*)-3-*methylpyrazole.*—This was prepared from 5-methoxy-2-acetoacetylphenol (1 g.) as in the previous case. The 1-*phenyl*-5-(2-*hydroxy*-4-*methoxyphenyl*)-3-*methylpyrazole* (1·9 g.) crystallised from the cooled reaction mixture and separated from alcohol in opaque prisms, m. p. 155° (Found, in material dried at 110° in a vacuum over phosphoric anhydride: C, 72·2; H, 5·7; N, 10·5. $C_{17}H_{16}O_3N_2$ requires C, 72·9; H, 5·7; N, 10·0%). Its properties were similar to those of the previous pyrazole.

1-*Phenyl*-5-(2-*hydroxy*-4-*methoxyphenyl*)-3-*methylpyrazoline.*—A mixture of 2-hydroxy-4-methoxystyryl methyl ketone (2 g.; McGookin and Sinclair, *J.*, 1926, 1580), alcohol (30 c.c.), water (50 c.c.), and phenylhydrazine (1 g.) was boiled and allowed to cool slowly. The oily product was washed and crystallised from methyl alcohol and then from dilute methyl alcohol (charcoal), giving 1-*phenyl*-5-(2-*hydroxy*-4-*methoxyphenyl*)-3-*methylpyrazoline* as square plates, m. p. 149° (Found: C, 72·1; H, 6·4. $C_{17}H_{18}O_3N_2$ requires C, 72·3; H, 6·4%). It is soluble in dilute sodium hydroxide and gives a deep red ferric chloride reaction which rapidly changes to yellow-green. Its colourless solution in concentrated sulphuric acid becomes deep purple on addition of ferric chloride.

7-*Methoxy*-2-*methyl*-4-*thionchromone.*—7-Methoxy-2-methylchromone (9 g.) and phosphorus pentasulphide (9 g.) were heated at 120—130° for ½ hour, and the product was repeatedly extracted with boiling benzene (8 times with 100 c.c.), and the extracts united, treated with charcoal, filtered, and distilled. The residue (2 g.) separated from alcohol in pale orange-red needles, m. p. 146° (Found: C, 63·7; H, 4·5; S, 15·7. $C_{11}H_{10}O_2S$ requires C, 64·1; H, 4·9; S, 15·5%). This 7-*methoxy*-2-*methyl*-4-*thionchromone* (0·2 g.) was heated under reflux in alcohol (8 c.c.) with phenylhydrazine (0·15 g.) and 2N-sodium hydroxide (2 drops) for 1½ hours, cooled, and a few drops of concentrated hydrochloric acid added. The crystals which separated at 0° were collected, washed with water, and the crystalline residue (0·01 g.) was recrystallised from alcohol, giving crystals which became opaque on drying, and had m. p. and mixed m. p. with a specimen of 1-phenyl-5-(2-hydroxy-4-methoxyphenyl)-3-methylpyrazole 152—153°.

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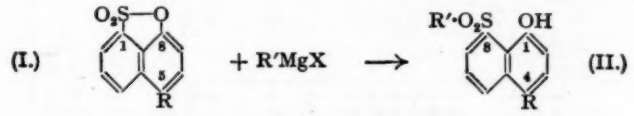
456. *Action of Grignard Solutions. Part III.* Action of Grignard Solutions on Naphthasultone and its Substituted Derivatives.*

By Ahmed Mustafa.

The action of Grignard solutions on naphthasultone (I; R = H) and its 5-methyl, 5-phenylsulphonyl, and 5-toluene-*p*-sulphonyl derivatives leads to a number of new *peri*-compounds, namely hydroxydiaryl sulphones (II). These react readily with ethereal diazomethane in the absence of methyl alcohol to form the corresponding methyl ethers.

In Part I (Mustafa and Gad, this vol., p. 384) it was shown that the action of Grignard solutions on tolylene-3 : 4-sulphonylide and naphthasultone (8-hydroxynaphthalene-1-sulphonic acid sultone) (I; R = H) provides a new method of preparing *o*-hydroxydiaryl sulphones and the corresponding *peri*-compounds. The reaction has been further investigated and a number of new *peri*-compounds has been synthesised.

8-Methylsulphonyl-, 8-ethylsulphonyl-, and 8-*tert.*-butylsulphonyl-1-naphthol were obtained by the action of the methyl-, ethyl-, and *tert.*-butyl-magnesium halide, respectively, on naphthasultone (I; R = H), followed by hydrolysis, and 8-ethylsulphonyl-4-methyl-, 8-phenylsulphonyl-4-methyl-, 8-methylsulphonyl-4-methyl-, and 8-1′-naphthylsulphonyl-4-methyl-1-naphthol by the action of the appropriate Grignard reagent on 5-methylnaphthasultone (I; R = Me). In an analogous way, use of 5-phenylsulphonyl- or 5-toluene-*p*-sulphonyl-naphthasultone as starting material led to the disulphonylnaphthols recorded in the table (overleaf).



The constitution of the products follows from the facts that they are colourless, react with ethereal diazomethane in the absence of methyl alcohol to form the corresponding methyl ethers (cf. Schonberg and Mustafa, *J.*, 1948, 605), dissolve in aqueous alkali, and contain active hydrogen.

The action of Grignard solutions on the sultones is an example of the breaking of the S–O linkage by this reagent. The application of the method for the synthesis of *o*-hydroxydiaryl sulphones and corresponding *peri*-compounds is under further investigation.

Experimental.

Action of Grignard Solutions on Naphthasultones.—The following exemplifies the procedure. Naphthasultone (I; R = H) (Erdmann, *Annalen*, 1888, **247**, 306) (3·5 g.) in dry benzene (50 c.c.) was added to a solution of *tert.*-butylmagnesium bromide [prepared from magnesium (1 g.), *tert.*-butyl bromide (14 g.), and dry ether (40 c.c.)], and the mixture was heated under reflux for 4 hours and then set aside overnight. The complex which separated was filtered off, decomposed with cold dilute hydrochloric acid, and extracted with ether. The ethereal solution was dried, the solvent evaporated, and the residue washed twice with cold light petroleum (b. p. 30—50°) and then with hot benzene (*ca.* 15 c.c.). The 8-tert.-*butylsulphonyl*-1-*naphthol* (3·5 g., *ca.* 75%) obtained was filtered off and crystallised (cf. the table).

The *naphthols* listed in the table were prepared similarly (for the compound in which R = $PhSO_2$ and R′ = Ph heating was for only 3 hours); except for methylmagnesium iodide, the Grignard reagents were bromides.

The naphthols dissolve in cold aqueous sodium hydroxide to give yellow solutions. In general they dissolve in hot alcohol, benzene, or acetone, but are sparingly soluble in light petroleum (b. p. 30—50°); the di- are less soluble than the mono-sulphonyl compounds.

Methylation.—This was effected by ethereal diazomethane (prepared from 8 g. of nitrosomethylurea) during 24 hours at 0°. The reaction mixture was evaporated, and an ethereal solution of the residue was treated with aqueous potassium hydroxide (to remove unchanged naphthol) and then with water, dried, and evaporated. The *ethers* prepared are recorded in the table. They are insoluble in aqueous alkali and give no colour in concentrated sulphuric acid. They are rather more soluble than the parent naphthols in organic solvents.

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* Part II, this vol., p. 1662.

		Naphthols (II).									Methyl ethers of (II).								
			Solvent	Colour	Found, %.				Required, %.			Solvent	Found, %.				Required, %.		
R.	R′.	M. p.*	for crystn.	in H_2SO_4.	C.	H.	S.	Formula.	C.	H.	S.	M. p.*	for crystn.	C.	H.	S.	Formula.	C.	H.	S.
H	Me	150°	A	yellow	59·3	4·5	14·1	$C_{11}H_{10}O_3S$	59·4	4·5	14·4	138—139°	A	61·0	5·1	12·9	$C_{12}H_{12}O_3S$	61·0	5·1	13·5
H	Et	210	B	,,	60·8	5·0	13·3	$C_{12}H_{12}O_3S$	61·0	5·1	13·5	146	A	62·2	5·5	12·5	$C_{13}H_{14}O_3S$	62·4	5·6	12·8
H	Bu^t	240 (pale brown)	B	none	63·5	5·9	12·0	$C_{14}H_{16}O_3S$ [a]	63·5	6·1	12·1	205—206 (pale yellow)	B or C	64·5	6·3	11·3	$C_{15}H_{18}O_3S$	64·7	6·5	11·5
Me	Me	155	C	yellow	60·7	4·9	13·4	$C_{12}H_{12}O_3S$	61·0	5·1	13·5	125	G	62·2	5·4	12·4	$C_{13}H_{14}O_3S$	62·4	5·6	12·8
Me	Et	158	D	,,	62·3	5·6	12·6	$C_{13}H_{14}O_3S$	62·4	5·6	12·8	126	G	63·3	6·0	11·9	$C_{14}H_{16}O_3S$	63·6	6·1	12·1
Me	Ph	170	D	,,	68·1	4·5	10·6	$C_{17}H_{14}O_3S$ [b]	68·4	4·7	10·7	147	A	68·9	5·0	10·1	$C_{18}H_{16}O_3S$	69·2	5·1	10·3
Me	1-$C_{10}H_7$	180	E	,,	72·0	4·5	8·9	$C_{21}H_{16}O_3S$	72·4	3·6	9·2	133	F	72·8	4·9	8·7	$C_{22}H_{18}O_3S$	72·9	4·9	8·8
$PhSO_2$	Bu^t	148—149	F	none	59·3	4·7	15·6	$C_{20}H_{20}O_5S_2$	59·4	4·9	15·8	—	—	—	—	—	—	—	—	—
$PhSO_2$	Ph	282 (brown)	B	,,	62·2	3·7	14·9	$C_{22}H_{16}O_5S_2$ [c]	62·3	3·9	15·1	—	—	—	—	—	—	—	—	—
$PhSO_2$	*p*-tolyl	237—238	B	pale brown	62·95	4·0	14·5	$C_{23}H_{18}O_5S_2$	63·0	4·1	14·6	—	—	—	—	—	—	—	—	—
$PhSO_2$	1-$C_{10}H_7$	218 (pale yellow)	B	none	65·9	3·7	13·4	$C_{26}H_{18}O_5S_2$ [d]	65·8	3·8	13·5	148	B	66·2	4·0	12·9	$C_{27}H_{20}O_5S_2$ [g]	66·4	4·1	13·1
Tos †	Me	146	B	—	57·2	4·3	16·8	$C_{18}H_{16}O_5S_2$	57·4	4·3	17·0	96	B	58·4	4·4	16·3	$C_{19}H_{18}O_5S_2$ [h]	58·5	4·6	16·4
Tos	Ph	260	B	none	62·9	3·9	14·3	$C_{23}H_{18}O_5S_2$	63·0	4·1	14·6	205	A	63·5	4·4	14·0	$C_{23}H_{18}O_5S_2$	63·8	4·4	14·2
Tos	Tos	247—248	—	—	63·7	4·2	14·1	$C_{24}H_{20}O_5S_2$ [e]	63·8	4·4	14·2	232—233	C	64·2	4·5	13·4	$C_{25}H_{22}O_5S_2$ [i]	64·4	4·7	13·7

* Colours are those of the melts. † Toluene-*p*-sulphonyl.

Solvents: A, methyl alcohol; B, benzene; C, ethyl alcohol; D, benzene–light petroleum (b. p. 30—50°); E, benzene–ethyl alcohol; F, light petroleum (b. p. 30–50°) (slow evaporation); G, light petroleum, (b. p. 100—110°).

[a] Active H: found, 0·37; required, 0·38%. [b] Active H: found, 0·32; required, 0·33%. [c] Found: active H, 0·23%; *M*, 417. Required: active H, 0·24%; *M*, 424. [d] *M*: found, 465; required, 474. [e] *M*: found, 446; required 452. [g] OMe: found, 11·0; required 11·2%. [h] OMe: found, 6·3; required, 6·4%. [i] OMe: found, 7·6; required, 7·9%. [j] OMe: found, 6·5; required, 6·7%.

457. *The Resolution of Methylisobutylcarbinol.*

By J. Kenyon and H. E. Strauss.

Dextrorotatory methyl*iso*butylcarbinol, in an optically pure form and in good yield, can be conveniently obtained from the commercially available (±)-carbinol.

In order to increase the relatively small number of organic compounds of simple structure which can be conveniently prepared in an optically pure condition in amounts suitable for experimental investigations, we have examined the resolution of methyl*iso*butylcarbinol (4-methylpentan-2-ol) which has recently become commercially available at low cost.

The resolution of this alcohol was described by Pickard and Kenyon (*J.*, 1911, **99**, 45), but as the description of procedure is far too brief we have given it with the added necessary details in the experimental section of this communication.

Two crystallisations of the brucine salt of methyl*iso*butylcarbinyl hydrogen phthalate are sufficient to yield the optically pure (+)-carbinol, but we were unable, as were Pickard and Kenyon (*loc. cit.*), to prepare a second alkaloidal salt of this ester, which would effect the separation of optically pure (−)-methyl*iso*butylcarbinol.

Since Pickard and Kenyon (*loc. cit.*) found that fractional crystallisation of the brucine and the cinchonidine salt of the hydrogen succinate yielded respectively the (−)- and the (+)-carbinol, the rotatory powers of which were equal in magnitude and almost identical with that of the (+)-carbinol prepared by the method herein described, it seems highly probable that optical purity has been attained.

Observed Rotatory Powers of (+)-Methylisobutylcarbinol for Various Wave-lengths (l, 2·00; t, 19·5°).

λ, A.	6438	5893	5461	5086	4800	4678	4358	4078
α	+28·29°	+34·22°	+40·27°	+46·77°	+52·97°	+56·12°	+65·48°	+76·3°

The values of λ^2, plotted against $1/\alpha$, lie on a straight line.

It is interesting to record that a specimen of (−)-methyl*iso*butylcarbinol which had $[\alpha]_{5893}^{17}$ −20·80° when prepared in 1909 had $[\alpha]_{5893}^{17}$ −19·54° after being kept in a stoppered bottle for 40 years.

Experimental.

Commercial methyl*iso*butylcarbinol was dried (K_2CO_3) and distilled through a 6-inch column; it distilled almost completely at 130·5—131°.

(±)-*Methylisobutylcarbinyl Hydrogen Phthalate.*—A mixture of the alcohol (112 g.), phthalic anhydride (163 g.), and pyridine (88 g.) was heated on the steam-bath until it became homogeneous. Next day the resultant oil was dissolved in acetone (300 c.c.) and mixed with dilute hydrochloric acid (140 c.c. of concentrated acid plus 140 c.c. of ice and water), the whole being well stirred. The solution was then diluted with ice and water (3—4 l.) until the oily hydrogen phthalate was completely precipitated. The mixture was set aside for 2 days with occasional stirring, during which time the aqueous layer was twice decanted and replaced by water to which hydrochloric acid (10 c.c.) had been added. The solidified acid ester was dissolved in aqueous sodium carbonate, and the solution extracted with ether to remove a little unesterified carbinol. The aqueous layer was acidified with hydrochloric acid, and the liberated acid ester extracted with ether. The ethereal extract was washed 12 times with dilute hydrochloric acid to ensure complete removal of pyridine.

Evaporation of the dried ethereal solution yielded (±)-methyl*iso*butylcarbinyl hydrogen phthalate (255 g., 93%) as an oil which readily set to a hard crystalline mass when inoculated. A " seed " was obtained by placing a little of the oil, contained in a vacuum desiccator, in a refrigerator overnight. It melts at 43—44° and is too soluble in the usual solvents for convenient recrystallisation. Unless the method of purification, outlined above, is followed, the compound will not crystallise.

(+)-*Methylisobutylcarbinyl Hydrogen Phthalate.*—Brucine (466 g. of the tetrahydrate) was added quickly to a hot solution of the (±)-ester (250 g.) in acetone (3·1 l.). On cooling, a crop (*A*) of crystalline brucine salt readily separated. This after one recrystallisation from acetone yielded crop (*B*) (191 g.) of optically pure brucine salt of (+)-methyl*iso*butylcarbinyl hydrogen phthalate, m. p. 167—168°. By concentration of the mother-liquor from crop (*B*) and recrystallisation of the salt which separated, a further 36 g. of pure brucine salt were obtained.

The brucine salt (226 g.) was decomposed by adding it to a mechanically stirred mixture of acetone (350 c.c.), water (200 c.c.), and concentrated hydrochloric acid (55 c.c.). The resultant product was diluted with water (3 l.), whereupon the brucine hydrochloride dissolved and the acid ester separated as an oil. This (83·5 g., 67%) was removed by means of ether and crystallised rapidly when inoculated with the (±)-ester; it had m. p. 44·5—46°, was too soluble for recrystallisation, and had $[\alpha]_{5893}^{20}$ +51·01° and $[\alpha]_{5461}^{20}$ +61·72° (*c*, 5·000; *l*, 2 in chloroform).

(+)-*Methylisobutylcarbinol.*—A current of steam was passed through a solution of the (+)-acid ester (82·4 g.) and potassium hydroxide (46 g.) in water (200 c.c.). The steam distillate yielded (+)-methyl-*iso*butylcarbinol (28·1 g.), b. p. 63—64°/45 mm., $d_4^{19\cdot5}$ 0·8075, $\alpha_{5893}^{19\cdot5}$ +34·22° (*l*, 2).

(−)-*Methylisobutylcarbinol.* The filtrate left after removal of crop (*A*) of the brucine salt was

concentrated to *ca.* 700 c.c. and mixed with concentrated hydrochloric acid (80 c.c.) and ice-water (160 c.c.), and the product, after dilution with water (3 l.), extracted with ether. The resultant hydrogen phthalate (140·5 g.) had $[\alpha]_{5893}$ −31·2° in chloroform and, when hydrolysed with potassium hydroxide (79 g.), yielded the partly resolved carbinol (45·7 g.), b. p. 64—65°/45 mm., $\alpha_{5893}^{19\cdot5}$ −20·95° (*l*, 2).

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458. *The Configuration of Naturally Occurring Mixed Glycerides. Part V. The Configuration of the Major Component Glycerides of Cacao Butter.*

By M. L. MEARA.

Cacao butter has been resolved into eleven fractions by exhaustive crystallisation. From a knowledge of the component fatty acids of each fraction the component glycerides are deduced, and from these and from the data obtained on crystallising hydrogenated portions of selected fractions the presence of β-oleodistearin, β-palmito-oleostearin, β-oleodipalmitin, and β-palmito-diolein have been unequivocally proved. It is possible that α-oleodipalmitin may also be present in small amounts.

CACAO butter, although it melts below 35°, is particularly hard and brittle and softens over a narrow temperature range. It is therefore not surprising that this is a commercially valuable confectionery fat, and has been the subject of a number of investigations. Klimont (*Z. Unters. Nahr. Genussm.*, 1906, **12**, 359) isolated an oleodistearin, an oleodipalmitin, and an oleopalmito-stearin from this fat, and showed that simple triglycerides were absent. Amberger and Bauch (*ibid.*, 1924, **48**, 371) fractionally crystallised a hydrogenated cacao butter, the data obtained, as subsequently interpreted by Lewkowitsch (*J. Soc. Chem. Ind.*, 1933, **52**, 236T), indicating the presence of 56% of α-palmito-oleostearin, 26·5% of β-oleodistearin and 17·5% of β-palmito-diolein. A more comprehensive study was carried out by Hilditch and Stainsby (*J. Soc. Chem. Ind.*, 1936, **35**, 95T) who separated cacao butter by crystallisation into three fractions. The component fatty acids of each fraction were determined, and from these the component glycerides were deduced to be oleopalmitostearins 52, oleodistearins 19, stearodioleins 12, palmitodioleins 9, oleodipalmitins 6, palmitostearins 2% (wt.). Further they were able to isolate large amounts of β-palmitodistearin from completely hydrogenated and partly hydrogenated specimens of cacao butter. They concluded that oleopalmitostearin occurred primarily as the β-palmito-isomer, and put forward a certain amount of evidence to show that β-oleodipalmitin and β-oleodistearin were present, and also suggested the possible occurrence of both α- and β-stearodiolein in cacao butter.

The present paper constitutes an attempt to isolate individual component glycerides in a state of sufficient purity for them to be examined by the methods developed in Parts I—IV of this series (*J.*, 1945, 22, 23; 1947, 773; 1948, 722).

EXPERIMENTAL.

Neutralised cacao butter (*ca.* 600 g.; saponification equiv., 290·0; I.V., 36·7; component fatty acids, mol.-%: palmitic 26·2, stearic 34·4, oleic 37·3, and linoleic 2·1) was exhaustively crystallised from acetone and ether at various dilutions and temperatures in a manner somewhat similar to that described in Part IV of this series. As was expected the crystallisation required was more exhaustive than that necessary for piqui-a fruit coat fat (Part III) and palm oil (Part IV) since the larger number of component glycerides renders the separations obtained on crystallisation much less complete, apparently in consequence of mutual solubility effects. Such effects have also recently been found to be acute in the case of Dika fat (component fatty acids: decoic 2·0, lauric 46·6, myristic 44·1, palmitic 5·2 oleic 1·9, linoleic 0·2 mol.-%.

The fat was finally resolved into eleven fractions (see Tables I and II). The component fatty acids of each fraction were determined by ester fractionation after a preliminary lead salt separation, and the component glycerides computed from the data obtained.

TABLE I.

Fractions obtained on Crystallisation of Cacao Butter.

Fraction.	A.	B.	C.	D.	E.	F.	G.	H.*	I.	J.*	K.
Wt. (g.)	55·3	37·1	56·5	100·5	104·5	67·8	15·9	22·4	45·6	7·9	12·3
Sap. Equiv. ...	297·9	296·4	291·3	287·9	285·1	288·7	286·9	290·9	290·9	290·9	299·3
I.V.	27·4	26·8	28·9	28·8	29·5	34·1	46·3	52·4	56·2	59·0	79·8
% (wt.)	10·5	7·1	10·7	19·1	19·9	12·9	3·6	4·3	8·7	1·5	2·3
% (mol.)	10·2	6·9	10·7	19·3	20·2	13·0	3·1	4·2	8·6	1·5	2·3

TABLE II.

Component Acids and Glycerides of Cacao Butter Fractions.

Fraction.	A.	B.	C.	D.	E.	F.	G.	H.	I.	J.	K.	
Acid, mol.-% :												
palmitic	3·5	8·1	21·5	31·9	39·2	41·3	31·1	23·6	23·6	23·6	8·4	
stearic	64·4	60·6	45·6	35·9	28·5	26·0	21·9	17·8	17·8	17·8	8·9	
oleic	32·1	31·3	32·9	31·8	31·5	26·6	41·5	53·1	53·1	41·5	71·5	
linoleic	—	—	—	0·4	0·8	6·1	5·5	5·5	5·5	5·5	11·2	
Component glyceride groups, mol.-% :												
trisaturated	3·7	6·3	1·3	3·4	3·1	2·9	—	—	—	—	—	
disatd. mono-unsatd.	96·3	93·7	98·7	96·6	97·9	97·1	59·0	24·2	24·2	24·2	51·9	
mono-satd. di-unsatd.	—	—	—	—	—	—	41·0	75·8	75·8	75·8	48·1	
Component glycerides (increments, mol.-%) :												
fully saturated ...	0·4	0·4	0·1	0·7	0·6	0·4	—	—	—	—	—	2·6
oleopalmitostearin	0·8	1·2	6·8	17·5	16·4	9·7	1·6	0·9	1·8	0·3	—	57·0
oleodistearin	9·0	5·3	3·8	1·1	3·2	—	—	—	—	—	—	22·4
oleodipalmitin ...	—	—	—	—	—	2·9	0·3	0·1	0·3	0·1	—	3·7
palmitodiolein ...	—	—	—	—	—	—	0·7	1·8	3·7	0·6	0·6	7·4
stearodiolein	—	—	—	—	—	—	0·5	1·4	2·8	0·5	0·6	5·8
linoleodiolein	—	—	—	—	—	—	—	—	—	—	0·8	0·8
triolein	—	—	—	—	—	—	—	—	—	—	0·3	0·3

* The small fractions H and J are assumed to have the same composition as fraction I.

A portion of each fraction (other than the very small groups, G, H, J, and K) was hydrogenated at 100° in the presence of Raney nickel, after which the completely hydrogenated glycerides obtained were exhaustively crystallised from ether, following the procedures developed in Part IV (*loc. cit.*).

DISCUSSION.

In this investigation it was not possible, as in earlier studies, to separate fully saturated from mixed saturated-unsaturated glycerides. Consequently the accuracy of the computation of the fully saturated components depends in some instances upon any limitation in accuracy, resulting from analysis of relatively small amounts of each fraction, since an error of, *e.g.*, 1% in the component fatty acids may give rise to, *e.g.*, 3% error in terms of component glycerides. It is possible that analyses of small quantities of material tend to underestimate slightly the content of unsaturated acids.

Fraction A, which was obtained in well-defined crystalline form, consists almost entirely of an oleo-distearin which is capable of existence in polymorphic forms melting at 23—24°, 29—30°, 36·5—37°, 43·3—43·5°, respectively, indicating the presence of β-oleodistearin. Crystallisation of the hydrogenated material gave a small fraction AH3 consisting of pure β-palmito-distearin, indicating the presence of a small proportion of β-palmito-oleostearin in fraction A. From Tables II and III it is deduced that fractions B and C were not composed of single individual glycerides but contained oleodistearin in decreasing, and oleopalmitostearin in increasing, amount. The configuration of the oleodistearin in these fractions cannot be stated categorically but it is reasonable to suppose that, since it occurred exclusively as the β-oleo-isomer in fraction A, much if not all of that in fractions B and C can be expected to have had this configuration. The oleopalmitostearin in these fractions occurred exclusively as the β-palmito-isomer since only the symmetrical palmito-distearin was observed in the respective hydrogenated palmito-glyceride fractions. Fraction D consisted of a fairly pure specimen of oleopalmitostearin which on hydrogenation gave rise to β-palmitodistearin in amounts indicative again of the virtual absence of any of the α-isomer. Similarly, β-palmitodistearin was identified in quantity in the hydrogenated fraction E together with an indication of β-stearodipalmitin originating from β-oleodipalmitin which occurred to the extent of about 16% in this fraction. The possibility of the occurrence of α-stearodipalmitin in this fraction cannot be overlooked, but, since the m. p. of EH5, the fraction of lowest m. p., ranged from 63° to 66°, large amounts of this isomer cannot have been present, otherwise the m. p. would have been considerably depressed. In the same way fraction F is very similar to fraction E in that no difficulty was experienced in obtaining relatively large amounts of β-palmitodistearin (derived from β-palmito-oleostearin), and there was evidence of β-stearodipalmitin together with, possibly, small quantities of α-stearodipalmitin. Finally fraction IH1 clearly indicates the presence of

TABLE III.

Transition and Melting Points of Fractions obtained by Fractional Crystallisation of Hydrogenated Fractions.

	G.	% of fraction.	Polymorphic forms. IV.	III.	II.	I.	M. p.*
AH1	10·70	89·0	54·0	64—65	—	71·5—71·7	—
AH2	0·78	6·5	53·5—54	64—65	—	71·2—71·5	—
AH3	0·28	2·3	49—50	54—55	63—64	67·5—68	—
BH1	8·28	57·2	54·5	64—65	—	71—72	—
BH2	2·25	15·5	—	—	—	—	67—69°
BH3	1·70	11·7	49—50	54—55	63—64	67—68	—
BH4	0·53	3·7	—	—	—	—	65—67
CH1	4·89	27·9	53—54	63—65	—	70—71	—
CH2	4·68	26·7	—	—	—	—	67—68·5
CH3	4·53	26·3	49—50	54—55	63—64	67—67·5	—
CH4	0·80	4·6	—	—	—	—	65·5—67·5
CH5	0·78	4·4	—	—	—	—	64—67
CH6	0·95	5·4	—	—	—	—	64—66
DH1	6·94	36·0	50	55—56	63·5—64	67—67·8	—
DH2	2·01	10·4	49—50	55—56	63—64	67—67·5	—
DH3	3·68	19·1	49—50	54—55	63—64	66·5—67·5	—
DH4	1·44	7·5	—	—	—	—	66—67·5
DH5	2·61	13·6	—	—	—	—	64—66·5
EH1	4·81	25·4	49—50	55—56	63·5—64	67—68	—
EH2	4·18	22·2	49—50	54—55	63—64	66—67·5	—
EH3	1·95	10·3	48—49	54—55	63—64	66—67	—
EH4	3·67	19·4	—	—	—	—	64—66
EH5	1·90	10·0	—	—	—	—	63—66
FH1	4·92	33·4	49—50	55—56	64	67·5—68	—
FH2	2·91	19·7	49—50	55—56	63·5—64	67—68	—
FH3	0·97	6·6	49—50	54—55	63—64	67—67·5	—
FH4	0·88	5·9	—	—	—	—	66—67
FH5	0·80	5·4	—	—	—	—	65—66·5
FH6	0·76	5·2	—	—	—	—	64—66
IH1	3·70	25·5	54·0	64—65	—	71·5—72	—
IH2	2·07	14·3	—	—	—	—	67—69
IH3	2·55	17·6	49—50	55—56	63·5—64	67—68	—
IH4	0·95	6·5	49—50	54—55	63—64	66·5—67·5	—
IH5	0·55	3·8	—	—	—	—	64—66
β-Stearodipalmitin ‡			49	59	65	68	—
α-Stearodipalmitin ‖			46·5	55	59·5	62·5	—
β-Palmitodistearin ‡			50	56	64	68	—
α-Palmitodistearin ‖			50	57	61	65	—
Tristearin †			54·5	65	—	71·5	—

* Detailed thermal data were not determined for fractions which were binary mixtures, the melting points only being recorded.

† Clarkson and Malkin, *J.*, 1934, 666. ‡ Malkin and Meara, *J.*, 1939, 103.

‖ Carter and Malkin, *J.*, 1939, 577.

tristearin derived from stearodiolein. The bulk of the fraction IH2, IH3, IH4 consisted of β-palmitodistearin derived from β-palmito-oleostearin and β-palmitodiolein respectively, indicating that in both of these glycerides the palmitic acid is attached to the β-hydroxyl group of the glycerol. Fraction IH5 which consisted primarily of stearodipalmitin showed evidence of the presence of the β-isomer, but the absence of the α-isomer was not precluded.

It is clear therefore that in cacao butter, a seed fat as distinct from a fruit coat fat, there is but little evidence of the presence of unsymmetrical glycerides, the following glycerides having been unequivocally identified: β-oleodistearin, β-palmito-oleostearin, β-oleodipalmitin, and β-palmitodiolein. The presence of small amounts of α-oleodipalmitin is however not excluded.

In Part IV of this series it was shown that the estimate of the component glyceride composition obtained from exhaustive-crystallisation data was in good agreement with the values obtained by applying the appropriate method of computation.

In the present investigation it is possible to compare the values obtained for the constituent mixed triglycerides of cacao butter with those determined earlier by Hilditch and Stainsby (*loc. cit.*) and with the values computed on the basis of simple " even " distribution (cf. Hilditch and Meara, *J. Soc. Chem. Ind.*, 1942, **61**, 117), a modified " even " distribution, or " random " distribution of the fatty acids amongst the glycerol molecules.

TABLE IV.

Observed and Computed Composition of Cacao Butter.

	Found.		Computed.		
	Present investigation.	Hilditch & Stainsby.	" Even."	Modified " even."	" Random."
Fully saturated glycerides	2·6	2·5	—	—	24·0
Oleodipalmitin	3·7	6·5	—	9·6	8·4
Oleopalmitostearin	57·0	51·9	75·9	57·6	21·6
Oleodistearin	22·2	18·4	11·0	20·2	13·7
Palmitodiolein	7·4	8·4	5·8	5·8	11·3
Stearodiolein	5·8	12·0	7·3	7·3	15·8
Triolein	1·1	—	—	—	5·2

The two experimentally determined sets of values agree amongst themselves. Simple " even " distribution considerably over-estimates oleopalmitostearin, primarily at the expense of other mono-oleo-glycerides. " Random " distribution grossly over-estimates the fully saturated glyceride content and to some extent the di- and tri-oleins at the expense primarily of oleopalmitostearin and to a lesser extent oleodistearin.

If, however, after partitioning oleic acid between palmitic and stearic acids the assumption (first suggested by Hilditch and Stainsby, *loc. cit.*) is made that in the mono-oleo-portions only two-thirds of the oleic acid is associated with palmitic and stearic acids as oleopalmitostearin, the remainder occurring as oleodipalmitin and oleodistearin respectively, values are obtained which are in good agreement with the experimentally determined values.

Borneo tallow, another fat in which simple computation appears to give rise to an over-estimated amount of oleopalmitostearin, is at present under similar investigation.

The author thanks Professor T. P. Hilditch for his continued advice and criticism during this investigation.

THE UNIVERSITY, LIVERPOOL. [*Received, April 13th,* 1949.]

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459. *Flavonols from the Bark of* Melicope ternata. *Part I. The Isolation of Four New Flavonols, Meliternatin, Meliternin, Ternatin, and Wharangin.*

By LINDSAY H. BRIGGS and R. H. LOCKER.

Four new flavonols, ***meliternatin***, ***meliternin***, ***ternatin*** and ***wharangin***, of molecular formulæ $C_{19}H_{14}O_8$, $C_{20}H_{18}O_8$, $C_{19}H_{16}O_8$ and $C_{17}H_{12}O_8$ respectively, have been isolated from the bark of *Melicope ternata*. From degradative experiments definite formulæ, 3 : 5-dimethoxy-7 : 8 : 3′ : 4′-dimethylenedioxyflavone, 3 : 5 : 7 : 8-tetramethoxy-3′ : 4′-methylenedioxyflavone, and 5 : 4′-dihydroxy-3 : 7 : 8 : 3′-tetramethoxyflavone, are proposed for the first three compounds respectively, and a tentative formula is suggested for wharangin. Meliternatin and meliternin are unusual in being completely alkylated; the same two compounds and wharangin are unusual in containing methylenedioxy-groups, and meliternatin is unique in containing two such groups.

MELICOPE TERNATA (genus *Melicope*, order *Rutaceae*, Maori name " Wharangi ") is a small tree, 12—20 feet high, endemic to and occurring in both Islands of New Zealand, with other species in Australia, the Pacific Islands, and tropical Asia. The inner bark is bright yellow, aromatic, and bitter to the taste.

Following the isolation of coloured alkaloids, melicopine, melicopidine, and melicopicine from Australian *Melicope* species (Hughes, Lahey, Price, and Webb, *Nature*, 1948, **162**, 223), an examination of the bark of *Melicope ternata* first revealed the presence of two basic constituents which gave precipitates with the usual alkaloidal reagents and crystalline salts with acids. The compounds, however, contained no nitrogen and proved to be completely

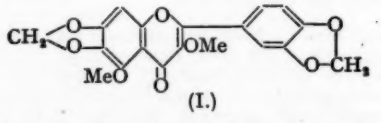
alkylated hydroxyflavones. Their basic properties were then utilised in the following method of extraction.

The dried bark was first extracted to completion with acetone, the acetone removed, and the residue completely extracted with trichloroethylene. Concentrated hydrochloric acid removed the completely alkylated flavones which were precipitated on dilution with water and separated by fractional crystallisation into flavonol *A*, $C_{19}H_{14}O_8$, and flavonol *B*, $C_{20}H_{18}O_8$. The trichloroethylene extract was then extracted successively with sodium hydrogen carbonate, sodium carbonate, and sodium hydroxide solution, and these were acidified. The hydrogen carbonate extract gave no crystalline material, the carbonate extract gave a third flavonol, flavonol *C*, $C_{17}H_{12}O_8$, purified by crystallisation, whilst the hydroxide solution furnished a mixture from which a fourth flavonol, flavonol *D*, $C_{19}H_{18}O_8$, and a crystalline non-flavone *compound*, $C_{16}H_{16}O_4$ (?), could be separated by fractional crystallisation. All four flavonols proved to be new compounds for which the names *meliternatin*, *meliternin*, *wharangin*, and *ternatin* are proposed for *A*, *B*, *C*, and *D*, respectively.

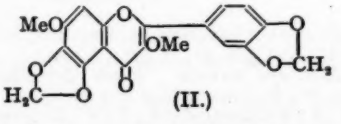
Meliternatin, $C_{19}H_{14}O_8$.—Meliternatin gives highly coloured solutions in concentrated mineral acids (from which it is precipitated on dilution), a crystalline hydrochloride, perchlorate, picrate, and picrolonate, and a precipitate with the usual alkaloidal reagents. It is insoluble in sodium hydroxide solution. It gives no colour with ferric chloride but a positive test for a methylenedioxy-group. Two methoxyl groups are present (Zeisel).

Reduction with magnesium and hydrochloric acid, as well as with sodium amalgam followed by acidification, gives the same salmon-pink colour. Asahina and Inubuse (*Ber.*, 1928, **61**, *B*, 1646) first found that flavones may be reduced to anthocyanidins only in alkaline solution, and flavonols only in acid solution, but flavanones in both acid and alkaline solution. This conclusion was later modified by the discovery (*Ber.*, 1929, **62**, *B*, 1256) that quercetin pentamethyl ether and rutin (quercetin-3-rhamnoglucoside) could be reduced in alkaline solution. We have extended this reaction and found that flavonols with a methoxyl group at $C_{(3)}$, in contrast with those with a free hydroxyl group at $C_{(3)}$, are reduced by sodium amalgam. The above reactions indicate that meliternatin is a flavone, and the molecular formula may then be accommodated by the presence of two methoxyl groups—one of them at $C_{(3)}$—and two methylenedioxy-groups.

Dealkylation with hydriodic acid afforded quercetagetin (3 : 5 : 6 : 7 : 3′ : 4′-hexahydroxyflavone), indicating two possibilities (I) and (II) for meliternatin. However, norwogonin dimethyl ether (7-hydroxy-5 : 8-dimethoxyflavone) and 7-hydroxy-5 : 8 : 4′-trimethoxyflavone are demethylated to baicalein (5 : 6 : 7-trihydroxyflavone) and scutellarein (5 : 6 : 7 : 4′-tetrahydroxyflavone), respectively, equivalent to the rearrangement of a 5 : 8- to a 5 : 6-configuration. Similarly 5 : 8-dimethoxyflavone is demethylated to 5 : 6-dihydroxyflavone with hydrobromic acid, but aluminium chloride as a dealkylating agent is free from this complication (for a summary, see Shah, Mehta, and Wheeler, *J.*, 1938, 1555). When aluminium chloride was used in this case an aluminium lake was produced from which, however, the aluminium could not be removed. The alternative, therefore, that meliternatin is a 5 : 7 : 8-derivative still remains for which there is only one possibility (III).

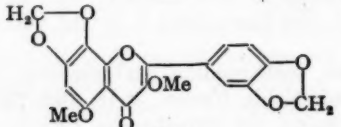


(I.)

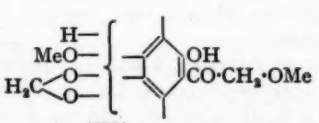


(II.)

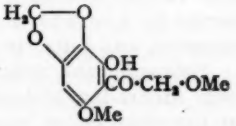
Hydrolysis of meliternatin with alcoholic potassium hydroxide yielded four products: piperonylic acid, which confirmed the structure of the side phenyl group, and three phenols. The structure of two of them adds little to the solution of the problem, but the third, $C_{11}H_{12}O_6$, obtained in greatest amount contains two methoxyl groups and a methylenedioxy-group and corresponds to the expected *compound* (IV).



(III.)



(IV.)



(V.)

The rigidly purified phenol gives a positive test with 2 : 6-dibromoquinonechloroimide

(Gibbs, *J. Biol. Chem.*, 1927, **72**, 649) indicating a free position *para* to the phenolic group. It must therefore have the structure (V), and the meliternatin structure must be (III).

Meliternin, $C_{20}H_{18}O_8$.—In its general properties meliternin reacts similarly to meliternatin but contains four methoxyl groups, the methylenedioxy-test again being positive. All the oxygen atoms are thus accounted for. Demethylation with hydriodic acid yielded gossypetin (3 : 5 : 7 : 8 : 3′ : 4′-hexahydroxyflavone). In this case the question of group migration does not occur, as rearrangements from a 5 : 6- to a 5 : 8-configuration have not been recorded. Hydrolysis with alcoholic potassium hydroxide gave piperonylic acid, establishing the structure of the side phenyl group and that of meliternin as (VI), which has now been confirmed by synthesis (succeeding paper).

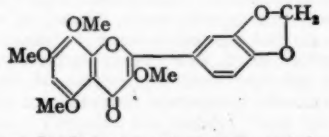
Ternatin, $C_{19}H_{18}O_8$.—Ternatin gives bright-yellow solutions with concentrated mineral acids but, although it is only slightly soluble in concentrated hydrochloric acid, its solution will give precipitates with alkaloidal reagents. It dissolves in aqueous sodium hydroxide but not in carbonate solution. It gives a green coloration with ferric chloride but the methylenedioxy-test is negative. It is reduced in acid or alkaline solution giving a strong reddish-violet colour, indicating a flavone with a methoxyl group at $C_{(3)}$. Four methoxyl groups are present, indicating a dihydroxy-tetramethoxy-flavone.

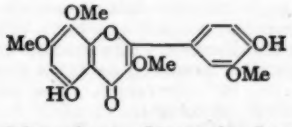
Demethylation with hydriodic acid gave quercetagetin, but here, as in the case of meliternatin, rearrangement may have occurred during the reaction. Methylation, however, with methyl sulphate and potassium carbonate afforded gossypetin hexamethyl ether where the question of rearrangement does not arise. There remains to be decided only the position of the free phenolic groups.

Hydrolysis of the diethyl ether with alcoholic potassium hydroxide yielded the ethyl ether of vanillic acid, proving the position of one free hydroxyl group at position 4′. Since ternatin has dyeing properties on mordanted wool it must have a free hydroxyl group at $C_{(3)}$ or $C_{(5)}$. Since the colour produced on alkaline reduction indicates a methoxyl group at $C_{(3)}$, the remaining hydroxyl group must be at $C_{(5)}$, and ternatin may be formulated as (VII). This has been confirmed by synthesis (forthcoming communication), and is also in harmony with the observation that in flavones containing hydroxy-groups in the 5 and 6, 7, or 8 positions which are partly methylated the position 5 is invariably unmethylated.

Wharangin, $C_{17}H_{12}O_8$.—Only 60 mg. of this compound were isolated and our constitutional deductions are based solely on colour reactions. This is the least basic compound of the series, being insoluble in concentrated hydrochloric acid, but dissolving in concentrated sulphuric acid to an intense yellowish-orange solution. On the other hand, it is more acidic than ternatin, dissolving in sodium carbonate as well as hydroxide solution. It gives a greenish-brown colour with ferric chloride, and the methylenedioxy-test is also positive. A strong salmon-pink colour is produced on acid or alkaline reduction, which indicates a flavonol methylated in position 3, this being the only methoxyl group shown as present by a Zeisel determination. Wharangin corresponds, therefore, to a trihydroxy-methoxy-methylenedioxy-flavone.

(VI.)

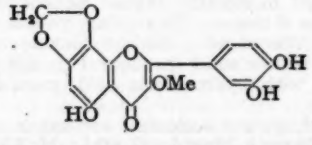


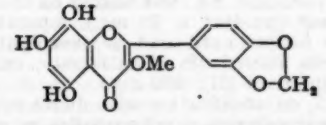


(VII.)

The three hydroxy-groups are not in vicinal position since wharangin does not give the Bargellini test (*Gazzetta*, 1919, **49**, ii, 47) characteristic of 5 : 6 : 7-trihydroxyflavones. Seshadri and Rao (*Proc. Ind. Acad. Sci.*, 1943, **17**, *A*, 20) have extended this reaction by reporting that norkanugin (3 : 7 : 3′ : 4′ : 5′-pentahydroxyflavone) also gives the test, whilst we have observed that anthragallol and areolatin (1 : 5 : 6 : 7-tetrahydroxy-2-methylanthraquinone) (*J.*, 1948, 599, 990) also gives positive tests.

(VIII.)





(IX.)

If on phytochemical grounds the same position is assumed for the oxygen atoms as in the three compounds already discussed, two formulæ (VIII) and (IX) are possible for wharangin.

A compound (IX) has been synthesised (succeeding paper), which does not agree in its properties with wharangin, for which we therefore suggest tentatively the formula (VIII).

It is interesting to note that of the four other completely alkylated flavones three of these, nobiletin (Tseng, *J.*, 1938, 1003; Robinson and Tseng, *ibid.*, 1938, 1004), tangeretin (Nelson, *J. Amer. Chem. Soc.*, 1934, **56**, 1392; Goldsworthy and Robinson, *J.*, 1937, 46) and aurantin (Patnayak, Rangawami, and Seshadri, *Proc. Ind. Acad. Sci.*, 1942, **16**, *A*, 10) occur in citrus species of the *Rutaceae*, of which *Melicope ternata* is a member, while the fourth, kanugin, from *Pongamia glabra* (*Leguminosae*) (Rao and Seshadri, *Proc. Ind. Acad. Sci.*, 1946, **23**, *A*, 147) is the only other naturally occurring flavone containing a methylenedioxy-group. ψ-Baptigenin, an *iso*flavone (Späth and Lederer, *Ber.*, 1930, **63**, *B*, 743), also contains a methylenedioxy-group. Meliternatin is unique in containing two such groups.

Experimental.

(M. p.s are corrected.)

Isolation of the Flavonols.—The bark was collected from mature trees at Papa Aroha, Coromandel. The air-dried powdered bark (2 kg.) was continuously extracted with acetone for 96 hours. After removal of the acetone, the residue was taken up in trichloroethylene, which was decanted later from a tarry deposit which settled out. The solution was then extracted with concentrated hydrochloric acid (10 × 200 c.c.), which next day was decanted from impurities. After dilution with 2 volumes of water, the acid layer was shaken with chloroform and separated from a further tarry deposit formed on dilution. The chloroform extract, a thick black tar, was dissolved in boiling dioxan and diluted with about its own volume of water. A black oil, which formed immediately, was removed by decantation and, from the solvent, a solid separated on cooling, contaminated with some oil. Fractional crystallisation of the solid from aqueous dioxan and then from alcohol afforded two products, flavonol *A* (*meliternatin*) and flavonol *B* (*meliternin*). The oil precipitated from the original dioxan–water mixture also yielded further material on trituration with alcohol. The total yield of meliternatin was 5·5 g. and that of meliternin 1 g.

The trichloroethylene layer was then extracted successively with saturated sodium hydrogen carbonate solution (5 × 500 c.c.), six times with almost saturated sodium carbonate solution and three times with 10% sodium hydroxide solution, and all the extracts were acidified. The oil separating from the hydrogen carbonate extract was dissolved in alcohol but no crystalline material could be obtained. The brown product from the carbonate extract yielded flavonol *C* (*wharangin*) (60 mg.) after crystallisation from alcohol and then from acetone. The product from the first hydroxide extract crystallised from alcohol to give flavonol *D* (*ternatin*), that from the third extract, compound *E*. All the products gave alternate crops of *D* and *E* on fractional crystallisation (yield of *D* and *E*, 260 and 160 mg., respectively).

Meliternatin could also be obtained readily from the bark by extraction first with boiling water and then with light petroleum (b. p. 40—60°) and working up the petroleum extract with acetone.

Meliternatin.—Meliternatin crystallises from alcohol in colourless needles, m. p. 198—198·5° (Found: C, 61·2; H, 4·0; OMe, 16·3. $C_{19}H_{14}O_8$ requires C, 61·6; H, 3·8; 2OMe, 16·8%). It is insoluble in hot or cold water and light petroleum, almost insoluble in ether, and soluble in the other usual organic solvents. A solution in concentrated sulphuric acid with a drop of 5% alcoholic gallic acid became yellowish-brown, but intense green overnight. The same test with phloroglucinol became first orange and overnight a clear orange-red, very sluggish tests compared with those of piperonal.

The hydrochloride was formed in bright yellow needles when a solution of meliternatin in concentrated hydrochloric acid was shaken or when hydrogen chloride was passed into its solution in benzene. The hydrochloride decomposes slowly when kept but rapidly when heated or when placed in a vacuum, reverting to meliternatin. When treated with hot perchloric acid it changes to orange-yellow but does not dissolve. The perchlorate formed needles, m. p. 223°, when purified from absolute alcohol. The picrate, prepared as for a base in alcohol solution, formed rosettes of slender yellow needles, m. p. ca. 90° (decomp.). The picrolonate, similarly prepared, formed mustard-coloured prisms, m. p. 127·5° (decomp.).

Dealkylation of Meliternatin to Quercetagetin.—Meliternatin (200 mg.) was heated for 2 hours at 150—155° with hydriodic acid (6 c.c., *d* 1·7) and phenol (3 c.c.) in an atmosphere of carbon dioxide. The yellow precipitate (160 mg.) formed on pouring the mixture into water, after repeated crystallisation from aqueous alcohol (2 : 1), formed clusters of mustard-coloured needles, m. p. 323° (decomp.), undepressed by an authentic specimen of quercetagetin, m. p. 324—325° (decomp.). The acetate, prepared by heating the dealkylated material (40 mg.) with acetic anhydride (0·2 c.c.) and pyridine (1 drop), was precipitated with and crystallised from alcohol, forming long, colourless, silky needles, m. p. 212—213°, undepressed by an authentic specimen of quercetagetin hexa-acetate of the same m. p.

Hydrolysis of Meliternatin.—Meliternatin (1 g.) dissolved in slightly diluted alcohol (35 c.c.) and potassium hydroxide (2 g.) was heated on the water-bath for 7 hours. On cooling, yellow needles of a potassium salt (product I, 70 mg.), separated and were filtered off. Carbon dioxide was bubbled through the filtrate until acid to phenolphthalein. The brown solid (product II; 420 mg.) which separated was filtered off. The filtrate, on acidification with hydrochloric acid, gave a colourless precipitate (product III; 430 mg.).

Product I, on acidification with dilute hydrochloric acid, gave a colourless substance, crystallising from acetone in pale cream, silky needles, m. p. 258—259° (26 mg.) [Found: C, 60·1; H, 3·7; OMe, 8·1. $C_{11}H_8O_5$ (?) requires C, 60·0; H, 3·6; OMe, 14·1%]. It gave a greenish-brown colour with ferric chloride, an intense green colour overnight with gallic acid in the methylenedioxy-test, but no reaction

with 2 : 6-dibromoquinonechloroimide (this may have been due to its insolubility in the buffer at pH 9·2). The composition of this compound does not correspond with any of the expected products.

Product II could not be induced to crystallise, but a portion readily sublimed at 100—120° in a high vacuum. The bright yellow, crystalline sublimate (250 mg.) then crystallised from alcohol in yellow prisms, m. p. 138·5—139·5° (mg.) (Found: C, 55·4; H, 5·65; OMe, 25·4. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0; 2OMe, 25·8%). This material gave a dark green colour with ferric chloride, and slowly a strong green colour in the methylenedioxy-test with gallic acid. A portion was thrice crystallised, twice from charcoal, and the cream-coloured prisms, m. p. 142—144°, then gave a strong violet colour in a few minutes with an aqueous suspension of 2 : 6-dibromoquinonechloroimide buffered at pH 9·2. These properties correspond with the expected structure of *2-hydroxy-6 : ω-dimethoxy-3 : 4-methylenedioxy-acetophenone.*

The residue from the sublimation was also resistant to crystallisation, but could readily be crystallised as its sodium salt from 10% sodium hydroxide solution. The yellow needles so obtained were dissolved in hot water, and the colourless product obtained after acidification was twice crystallised from alcohol to give long, colourless needles, m. p. 194—195° (33 mg.) [Found: C, 61·9; H, 4·7; OMe, 11·6. $C_{10}H_{10}O_4$ (?) requires C, 61·8; H, 5·1; 1OMe, 16·0%]. This material is soluble in sodium carbonate solution to give a yellow solution, and it gives no colour with ferric chloride and slowly an intense green colour in the methylenedioxy-test. The composition of this compound does not correspond with any of the expected products.

Product III was crystallised from alcohol, sublimed at 210° at atmospheric pressure, and recrystallised from the same solvent. The m. p. (230—231·5°) of the colourless prisms was undepressed by an authentic specimen of piperonylic acid.

Meliternin.—Meliternin crystallises from alcohol in colourless prisms, m. p. 185·5—186° (Found: C, 61·65; H, 4·6; OMe, 35·0. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7; 4OMe, 32·1%). It is insoluble in water, moderately soluble in alcohol and acetone, and soluble in chloroform, benzene, and dioxan. It gave only a slight green colour overnight in the methylenedioxy-test with gallic acid and an orange-red colour in the same test with phloroglucinol, but a reddish-brown colour was produced with concentrated sulphuric acid alone in the same period.

An orange amorphous hydrochloride formed when a solution of meliternin in benzene was treated with dry hydrogen chloride. Orange-red needles of a sulphate separated from an absolute alcoholic solution of meliternin when treated with concentrated sulphuric acid. Both salts decomposed immediately in contact with water and when kept. In concentrated hydrochloric acid meliternin gave coloured precipitates with the usual alkaloidal reagents. Reduction of an alcoholic solution with magnesium and hydrochloric acid or with sodium amalgam followed by acidification both gave an intense reddish-violet colour.

Dealkylation of Meliternin to Gossypetin.—Meliternin (100 mg.) was heated for 3 hours at 150—160° with hydriodic acid (3 c.c.; *d* 1·7) and phenol (1·5 c.c.). The product formed on pouring the mixture into water and crystallised repeatedly from aqueous alcohol (1 : 1) formed yellow needles, m. p. 304—305° (33 mg.). The dealkylated product was acetylated with excess of acetic anhydride and a drop of perchloric acid (60%) at room temperature. The product formed on pouring the mixture into water separated, after repeated crystallisation from methyl alcohol, in colourless needles, m. p. 229·5—231·5°. Perkin (*J.*, 1913, **103**, 650) records m. p. 228—230° for gossypetin hexa-acetate and Baker, Nodzu, and Robinson (*ibid.*, 1929, 74), m. p. 229—230°.

A small amount of this acetate was hydrolysed by dissolving it in concentrated sulphuric acid, setting the mixture aside for 10 minutes at room temperature and pouring it into water. The purified material then had m. p. 313—314°, undepressed by an authentic specimen of gossypetin. A solution of this material in a few drops of alcohol, added to a buffer of pH 9·8, rapidly changed from green to blue, a characteristic reaction of gossypetin and also of herbacetin and hibiscetin, all 3 : 5 : 7 : 8-poly-hydroxyflavones.

Hydrolysis of Meliternin.—A solution of meliternin (90 mg.) and potassium hydroxide (200 mg.) in 80% alcohol (2 c.c.) was heated on the water-bath for 8 hours. The alcohol was removed by distillation, the residue completely dissolved in water (4 c.c.), and carbon dioxide bubbled through the solution until it was acid to phenolphthalein. Extraction with ether afforded a small amount of yellow needles, but on attempted purification only a red oil was obtained. The residual aqueous solution was acidified and the precipitate (33 mg.), after repeated crystallisation from alcohol, formed colourless prisms, m. p 230—231·5°, undepressed by piperonylic acid.

Ternatin.—*Ternatin* crystallises from alcohol in yellow, silky needles, m. p. 210—210·5° (Found: C, 60·5; H, 4·9; OMe, 33·2. $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8; 4OMe, 33·2%). It is insoluble in water and light petroleum, moderately soluble in alcohol, and soluble in acetone.

An acetate of ternatin, obtained by acetic anhydride–pyridine, formed, after crystallisation from alcohol, pale cream-coloured needles, m. p. 165—166°, unreactive to ferric chloride solution. The acetate was photosensitive, however, and became orange on exposure to light.

Demethylation of Ternatin to Quercetagetin.—Ternatin (61 mg.) was heated for 3 hours at 150—160° with hydriodic acid (3 c.c.; *d* 1·7) and phenol (1·5 c.c.) in an atmosphere of carbon dioxide. The yellow precipitate (40 mg.), formed on pouring the mixture into water, crystallised from aqueous alcohol in yellow needles, m. p. *ca.* 306° (decomp.). The dealkylated product (21 mg.) was acetylated with acetic anhydride (0·2 c.c.) and 60% perchloric acid (1 drop) at room temperature for 2 hours. The product formed on pouring into water was crystallised successively from ethyl acetate and methyl alcohol, forming colourless prisms, m. p. 207—210°, undepressed by quercetagetin hexa-acetate.

Methylation of Ternatin to Gossypetin Hexamethyl Ether.—A solution of ternatin (60 mg.) in dry acetone (5 c.c.) was heated under reflux with anhydrous potassium carbonate (1 g.) and methyl sulphate (0·1 c.c.) for 6 hours. The acetone solution was filtered and concentrated to *ca.* 1 c.c. The colourless prisms separating on cooling (33 mg.) had, after two crystallisations from alcohol, m. p. 169—170°, undepressed by gossypetin hexamethyl ether, m. p. 170—171°.

Ternatin Diethyl Ether and its Hydrolysis.—Ternatin (100 mg.), dissolved in absolute alcohol (3 c.c.),

was ethylated by being heated under reflux with ethyl iodide (0·46 c.c.), potassium hydroxide (170 mg.) being added gradually during 6 hours. After a further hour's heating the excess of alcohol and ethyl iodide was distilled off and the product was repeatedly crystallised from alcohol to form almost colourless needles, m. p. 231·5—235·5° (46 mg.), giving no colour with ferric chloride.

A solution of ternatin diethyl ether (45 mg.) in 80% alcohol (2 c.c.) was heated with potassium hydroxide (340 mg.) for 6 hours. The alcohol was almost completely removed and carbon dioxide passed into an aqueous solution (5 c.c.) of the residue until it was acid to phenolphthalein. Brown needles of a potassium salt (12 mg.) separated, from which the free compound was liberated by dissolution in hot water and acidification with hydrochloric acid, whereupon long, fine, almost colourless needles separated, m. p. 150—151°, giving a brown colour with ferric chloride. This should be the unknown compound, 2-hydroxy-3 : 4 : ω-trimethoxy-6-ethoxyacetophenone but there was insufficient for analysis.

The residual aqueous solution was then acidified with hydrochloric acid. The product separating (7 mg.), after crystallisation from alcohol, formed colourless needles, m. p. 197—198°, undepressed by a synthetic sample of *O*-ethylvanillic acid of the same m. p.

Dyeing Properites of Ternatin.—A sample of wool mordanted with potassium dichromate and tannic acid was well washed with hot water and dyed by boiling it with a suspension of ternatin (*ca.* 2 mg.) in water (3 c.c.) for 10 minutes. The wool was dyed a pale mustard colour, unchanged after boiling with fresh water for 20 minutes.

Wharangin.—Wharangin crystallises from acetone in yellow needles, m. p. 277—278° (Found: C, 59·2; H, 3·8; OMe, 6·8. $C_{17}H_{12}O_8$ requires C, 59·3; H, 3·5; 1OMe, 9·0%). It is insoluble in water and light petroleum, and sparingly soluble in methyl and ethyl alcohol and acetone.

Compound E.—This compound crystallises from alcohol in colourless prisms or plates, m. p. 133·5—134° [Found: C, 70·2; H, 5·5; OMe, 11·8, 10·7%; *M*, 259, 288 (ebullioscopic in benzene). $C_{16}H_{16}O_4$ (?) requires C, 70·6; H, 5·9; 1OMe, 11·4%: *M*, 272]. It is insoluble in water and moderately soluble in alcohol. It dissolves in concentrated sulphuric acid with an orange solution but is insoluble in concentrated hydrochloric acid. Despite the fact that it was obtained by extraction with sodium hydroxide solution the purified material dissolves with the greatest difficulty in 10% hot or cold solution, giving a pale yellow solution. A faintly alkaline alcoholic solution shows a pale green fluorescence. The ferric chloride reaction is negative but the methylenedioxy-test with gallic acid gives an intense green colour overnight. No flavone test is given by acid or alkaline reducing agents, bromine in chloroform is decolorised immediately, whilst Brady's reagent gives no precipitate.

Absorption Spectra.—The absorption spectra of the new flavonols, compound *E*, and gossypetin hexamethyl ether and quercetagetin hexamethyl ether for comparison, were measured in *ca.* N/20,000 alcoholic solution in a Beckman spectrophotometer, Model DU, peaks being obtained as follows:

Compound.	λ.	log ε.	λ.	log ε.	λ.	log ε.
Meliternatin	249	4·24	269 *	4·11	336	4·40
Meliternin	253	4·33	272	4·24	350	4·27
Ternatin	258	4·31	273	4·28	368	4·26
Wharangin	261	4·32	273	4·27	377	4·27
Gossypetin hexamethyl ether	253	4·34	271	4·33	350	4·33
Quercetagetin hexamethyl ether	256	4·37	267 *	4·31	349	4·33
Compound *E*	227	4·30	269	4·34	346	4·07

* Points of inflexion.

The analyses are by Drs. Weiler and Strauss, Oxford, and Mr. R. N. Seelye of this department. We are indebted to the Chemical Society, the Royal Society of New Zealand, the Australian and New Zealand Association for the Advancement of Science, and the Research Grants Committee of the University of New Zealand for grants, and for a Research Scholarship to one of us (R. H. L.), to Dr. T. J. Sprott for measurement of some of the absorption spectra, and especially to Professor T. R. Seshadri for samples of quercetagetin and gossypetin derivatives and information concerning their colour reactions.

Auckland University College, Auckland, New Zealand. [*Received, April 13th*, 1949.]

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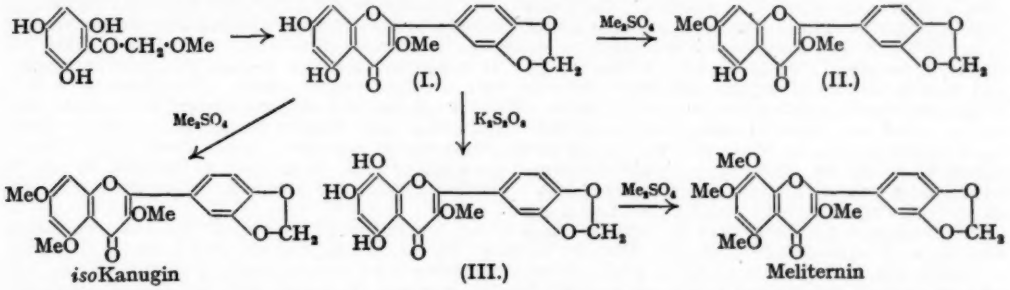
460. *Flavonols from the Bark of* Melicope ternata. *Part II. A Synthesis of Meliternin,* iso*Kanugin, and Allied Flavonols.*

By Lindsay H. Briggs and R. H. Locker.

Meliternin, *iso*kanugin, 5 : 8-*dihydroxy*-3-*methoxy*-3′ : 4′-*methylenedioxyflavone*, 5-*hydroxy*-3 : 8-*dimethoxy*-3′ : 4′-*methylenedioxyflavone*, and 5 : 7 : 8-*trihydroxy*-3-*methoxy*-3′ : 4′-*methylenedioxyflavone* have been synthesised by standard methods.

Using Allan and Robinson's flavonol synthesis (*J.*, 1924, 2192) and Rao and Seshadri's method of nuclear oxidation (*Proc. Indian Acad. Sci.*, 1947, **26**, 182 and earlier papers), meliternin (3 : 5 : 7 : 8-tetramethoxy-3′ : 4′-methylenedioxyflavone), *iso*kanugin (3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone), 5 : 7-*dihydroxy*-3-*methoxy*-3′ : 4′-*methylenedioxyflavone*, 5-*hydroxy*-3 : 7-

dimethoxy-3′ : 4′-methylenedioxyflavone and **5 : 7 : 8-*trihydroxy*-3-*methoxy*-3′ : 4′-*methylenedioxy*-*flavone*** have been synthesised according to the annexed scheme.



Condensation of 2 : 4 : 6-trihydroxy-ω-methoxyacetophenone with piperonylic anhydride in the presence of potassium piperonylate at 170—180° in a vacuum afforded 5 : 8-dihydroxy-3-methoxy-3′ : 4′-methylenedioxyflavone (I), converted by partial methylation into 5-hydroxy-3 : 8-dimethoxy-3′ : 4′-methylenedioxyflavone (II) and by complete methylation into *iso*kanugin (3 : 5 : 8-trimethoxy-3′ : 4′-methylenedioxyflavone) whose identity with the natural product was confirmed by mixed melting point.

Nuclear oxidation of (I) with potassium persulphate introduced a phenolic group at $C_{(8)}$ forming 5 : 7 : 8-trihydroxy-3-methoxy-3′ : 4′-methylenedioxyflavone (III) which, on complete methylation, produced 3 : 5 : 7 : 8-tetramethoxy-3′ : 4′-methylenedioxyflavone, identical in all respects with meliternin, the structure of which, suggested in Part I (preceding paper), is thus confirmed.

Experimental.

(M. p.s are corrected.)

5 : 7-*Dihydroxy*-3-*methoxy*-3′ : 4′-*methylenedioxyflavone*.—2 : 4 : 6-Trihydroxy-ω-methoxyacetophenone (5 g.; Slater and Stephen, *J.*, 1920, 312), piperonylic anhydride (20 g.; Rao and Seshadri, *Proc. Ind. Acad. Sci.*, 1946, **23**, 148), and potassium piperonylate (8·5 g.) were ground together and heated at 170—180°/25 mm. for 2 hours. The purple reaction mass was ground and boiled with 10% aqueous alcoholic (1 : 10) potassium hydroxide (300 c.c.) for 15 minutes. The pasty mass of yellow crystals, formed after removal of the solvent in a vacuum, was dissolved in water (500 c.c.), and carbon dioxide bubbled into the solution until it was acid to phenolphthalein. The precipitated solid (4·9 g.), after repeated crystallisation from acetone, formed yellow needles, m. p. 273·5—274·5°, of **5 : 7-*dihydroxy*-3-*methoxy*-3′ : 4′-*methylenedioxyflavone*** (Found: C, 61·8; H, 4·0; OMe, 8·6. $C_{17}H_{12}O_7$ requires C, 62·2; H, 3·6; 1OMe, 9·45%). It dissolves in sodium hydroxide, but not in carbonate, solution with a yellow colour. Reduction with magnesium and hydrochloric acid as well as with sodium amalgam followed by acidification gave a strong scarlet colour. Its bright-yellow solution in concentrated sulphuric acid rapidly became green on addition of gallic acid. It gave a stable pale yellow colour in a buffer at pH 9·8, and a brown colour with ferric chloride solution.

The ***diacetate***, formed by acetylating the flavone (20 mg.) with excess of acetic anhydride and 60% perchloric acid (1 drop) for ½ hour and pouring the mixture into water, crystallised from methyl alcohol in slender, colourless needles, m. p. 188·5° (14 mg.) (Found: C, 61·4; H, 3·9. $C_{21}H_{16}O_9$ requires C, 61·2; H, 3·9%).

5-*Hydroxy*-3 : 7-*dimethoxy*-3′ : 4′-*methylenedioxyflavone*.—5 : 7-Dihydroxy-3-methoxy-3′ : 4′-methylenedioxyflavone (800 mg.), dissolved in acetone (50 c.c.), was heated under reflux with methyl sulphate (0·27 c.c.) and anhydrous potassium carbonate (3·0 g.) for 6 hours. The solution was filtered, concentrated until crystallisation set in, and allowed to cool. The yellow needles produced (610 mg.), after repeated crystallisation from alcohol, had m. p. 183·5° (Found: C, 63·5; H, 4·55. $C_{18}H_{14}O_7$ requires C, 63·2; H, 4·1%. The partly methylated flavone is insoluble in concentrated hydrochloric acid and in both sodium carbonate and hydroxide (10%) solutions. It gives a brown colour with ferric chloride solution and a scarlet colour on acid and alkaline reduction.

One drop of perchloric acid (60%) was added to a mixture of the flavone (26 mg.) in acetic anhydride (0·5 c.c.). A red colour was produced but complete dissolution did not occur even on the addition of a further c.c. of acetic anhydride. The yellow insoluble plates formed after ½ hour were probably the perchlorate of the acetylated flavone. After the mixture had been poured into water to decompose the perchlorate, the ***acetate***, repeatedly crystallised from alcohol, formed slender, colourless needles, m. p. 192—193° (Found: C, 62·7; H, 4·5. $C_{20}H_{16}O_8$ requires C, 62·5; H, 4·2%).

iso***Kanugin***.—5 : 7-Dihydroxy-3-methoxy-3′ : 4′-methylenedioxyflavone (100 mg.), dissolved in acetone (15 c.c.), was heated under reflux with methyl sulphate (0·4 c.c.) and anhydrous potassium carbonate (1 g.) for 6 hours. The solution was filtered, concentrated until crystallisation set in, and cooled. The product, *iso*kanugin (70 mg.), crystallised from alcohol in long, colourless, rectangular plates, m. p. 198—199°, undepressed by an authentic specimen kindly provided by Professor T. R. Seshadri. *iso*Kanugin is soluble in concentrated hydrochloric acid with an intense yellow colour.

5 : 7 : 8-*Trihydroxy*-3-*methoxy*-3′ : 4′-*methylenedioxyflavone*.—To a solution of 5 : 7-dihydroxy-3-methoxy-3′ : 4′-methylenedioxyflavone (1·5 g.) in sodium hydroxide (1·5 g.) and water (50 c.c.) was

added dropwise during 2 hours and with mechanical stirring a solution of potassium persulphate (2·5 g., 2 mols.) in water (50 c.c.). After the mixture had been kept overnight, the brown gelatinous precipitate was collected, shaken with dilute hydrochloric acid, and heated on the water-bath for ½ hour with a little sodium sulphite solution. On cooling, the chrome-yellow solid (683 mg.) was repeatedly crystallised from alcohol (charcoal), aqueous acetone, and again from alcohol, forming deep-yellow needles, m. p. 259°, of 5 : 7 : 8-*trihydroxy*-3-*methoxy*-3′ : 4′-*methylenedioxyflavone* (Found: C, 59·7; H, 3·8; OMe, 7·1. $C_{17}H_{12}O_8$ requires C, 59·3; H, 3·5; 1OMe, 9·0%). It is slightly soluble in sodium hydrogen carbonate, and readily soluble in sodium carbonate, solution with a bright yellow colour. The solution in 10% sodium hydroxide solution is violet-red in colour. When it was reduced with magnesium and hydrochloric acid in alcohol a wine-red colour was produced. Reduction with sodium amalgam in alcohol caused rapid decolorisation in dilute solution but in more concentrated solution copious green flocks formed, becoming yellow on warming, a colour unchanged on acidification. A solution in a buffer at pH 9·8 passed from yellow through brown to colourless. Ferric chloride gave a brown, whilst the methylenedioxy-test with gallic acid rapidly produced a green, colour.

The *triacetate*, produced as in the first case from 15 mg., crystallised from alcohol in slender, colourless needles, m. p. 213—213·5° (12·5 mg.) (Found: C, 58·8; H, 4·3. $C_{23}H_{18}O_{11}$ requires C, 58·7; H, 3·9%).

Meliternin.—A solution of 5 : 7 : 8-trihydroxy-3-methoxy-3′ : 4′-methylenedioxyflavone (90 mg.) in acetone (5 c.c.) was heated under reflux with methyl sulphate (0·15 c.c.) and anhydrous potassium carbonate (1·5 g.) for 5 hours. The acetone solution was filtered, concentrated to *ca.* 1 c.c., and cooled. Recrystallisation from alcohol of the prisms which formed (34 mg.) afforded almost colourless prisms, m. p. 184·5—185·5°, undepressed by a sample of natural meliternin.

Absorption Spectra.—The absorption spectra of the five synthetic flavonols and 5-hydroxy-3 : 7′ : 3′ : 4′-tetramethoxyflavone for comparison were measured in *ca.* N/20,000 alcoholic solution in a Beckman spectrophotometer, model DU, peaks being obtained as shown in the table. The absorption peaks of synthetic meliternin correspond with those of the natural product (Part I, *loc. cit.*).

Compound.	λ.	log ε.	λ.	log ε.	λ.	log ε.
5 : 7-Dihydroxy-3-methoxy-3′ : 4′-methylenedioxyflavone	250 *	4·23	262 *	4·15	335	4·32
5-Hydroxy-3 : 7-dimethoxy-3′ : 4′-methylenedioxyflavone	254	4·31	269 *	4·21	353	4·28
5 : 7 : 8-Trihydroxy-3-methoxy-3′ : 4′-methylenedioxyflavone	231	4·34	285	4·31	325	4·23
*iso*Kanugin	250	4·35	263 *	4·21	340	4·32
Meliternin (synthetic)	254	—	272	—	353	—
5-Hydroxy-3 : 7 : 3′ : 4′-tetramethoxyflavone	254	4·37	269	4·29	352	4·34

* Points of inflexion.

The analyses are by Drs. Weiler and Strauss, Oxford, and Mr. R. N. Seelye of this Department. We are indebted to the Chemical Society, the Royal Society of New Zealand, the Australian and New Zealand Association for the Advancement of Science, and the Research Grants Committee of the University of New Zealand for grants and for a Research Scholarship to one of us (R. H. L.).

Auckland University College, Auckland, New Zealand. [*Received, April 13th*, 1949.]

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461. *Basic Derivatives of Steroids.* 3-*Amino*-7 : 12-*dihydroxy-and* 3-*Amino*-12-*hydroxy-cholanic Acid.*

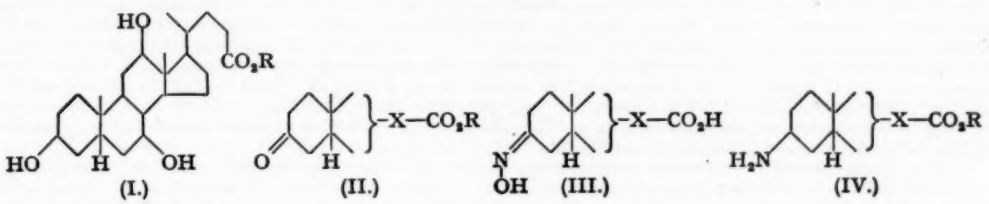
By A. S. Jones, M. Webb, and F. Smith.

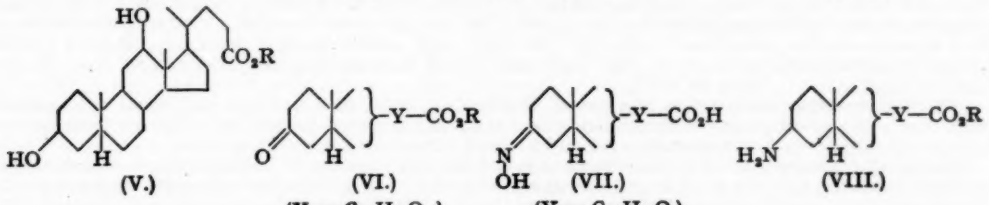
Oxidation of methyl cholate (I; R = Me) and methyl deoxycholate (V; R = Me) with aluminium *tert.*-butoxide effects preferential oxidation to the corresponding 3-keto-compounds. These keto-derivatives (II; R = Me) and (VI; R = Me) have been converted into oximes (III) and (VII), and these in turn have been transformed into 3-amino-7 : 12-dihydroxycholanic acid (IV; R = H) and 3-amino-12-hydroxycholanic acid (VIII; R = H), respectively. The bacteriostatic activities of these amino-acids and some of their esters against *Staph. aureus* and *Aerobacter aerogenes* have been determined; the *iso*amyl ester of 3-amino-7 : 12-dihydroxycholanic acid proved to be the most active.

Previous investigations of basic derivatives of cholesterol (Barnett, Ryman, and Smith, *J.*, 1946, 524, 528) and of cholane and norcholane (James, Smith, Stacey, and Webb, *J.*, 1946, 665) indicated that these substances have bacteriostatic activity. We have now extended this work to derivatives of hydroxycholanic acids, which possess an amino-group at $C_{(3)}$, namely, 3-amino-7 : 12-dihydroxycholanic acid (IV; R = H) and 3-amino-12-hydroxycholanic acid (VIII; R = H).

These amino-compounds were prepared by reduction of the oximes of the 3-keto-acids, the latter being derived by preferential oxidation of the 3-hydroxyl group with a mixture of aluminium *tert.*-butoxide and acetone (Oppenauer, *Rec. Trav. chim.*, 1937, **56**, 137). Thus methyl cholate (I; R = Me) and methyl deoxycholate (V; R = Me) yielded methyl 7 : 12-dihydroxy-3-keto-cholanate (II; R = Me) (cf. Kuwada and Morimoto, *Bull. Chem. Soc. Japan*, 1942, **17**, 147) and

methyl 12-hydroxy-3-ketocholanate (VI; R = Me) (cf. Riegel and McIntosh, *J. Amer. Chem. Soc.*, 1944, **66**, 1099), respectively, as the main products of the reaction. In each case, the oxidation was accompanied by the partial hydrolysis of the ester grouping which gave rise to a variable yield of the corresponding 3-keto-acid.





Although oxidation at $C_{(3)}$ may be facilitated by a Δ^5-ethenoid linkage (Barton and Jones, *J.*, 1943, 599; Inhoffen *et al.*, *Ber.*, 1938, **71**, 1024; Miescher and Klarer, *Helv. Chim. Acta*, 1939, **22**, 962; Butenandt and Schmidt-Thomé, *Ber.*, 1939, **72**, 182) this linkage appears not to be essential as oxidation of the saturated compounds (I; R = Me) and (V; R = Me) proceeds smoothly and appears to be confined to the 3-position (see Ehrenstein and Stevens, *J. Org. Chem.*, 1940, **5**, 660; Fuchs and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 511; Gallagher and Xenos, *J. Biol. Chem.*, 1946, **165**, 365). Moreover, the product is easy to isolate (cf. Gallagher, *ibid.*, 1940, **133**, xxxvi).

The identity of the methyl 7 : 12-dihydroxy-3-ketocholanate (II; R = Me) was established as described in the experimental section. Its hydrolysis afforded the *acid* (II; R = H), which crystallised from aqueous ethyl alcohol with or without alcohol of crystallisation, according to the concentration of ethyl alcohol in the solvent mixture.

The methyl 12-hydroxy-3-ketocholanate (VI; R = Me) was characterised by its m. p., the m. p. of the derived acid (VI; R = H), and the smooth conversion of the latter into the crystalline oxime (VII).

Reduction of the *oximes* (III) and (VII) with sodium in boiling amyl alcohol gave the corresponding 3-amino-compounds (IV; R = H) and (VIII; R = H), respectively, which were isolated as crystalline amino-acid *hydrochlorides*. The stereochemical arrangement of the group at $C_{(3)}$ in each case was not ascertained.

In an attempt to prepare 3-amino-7 : 12-dihydroxycholanic acid, 3-chloro-7 : 12-dihydroxycholanic acid was treated with ammonia (cf. Windaus and Adamla, *Ber.*, 1911, **44**, 3051). The experiment failed, however, and 7 : 12-dihydroxy-Δ^3-cholenic acid (Wieland, Honold, and Pascual-Vila, *Z. physiol. Chem.*, 1923, **130**, 326) was the main product of the reaction.

The *methyl* and the iso*amyl* ester (IV; R = Me and *iso*-C_5H_{11}) and the iso*amyl* ester (VIII; R = *iso*-C_5H_{11}) were prepared in the usual way, and their bacteriostatic activities against *Staph. aureus* and *Aerobact. aerogenes* were determined. In view of the marked activity of the iso*amyl ester* (IV; R = *iso*-C_5H_{11}) a further study of related substances is being pursued.

The bacteriostatic activities of the basic derivatives against *Staph. aureus* and *Aerobact. aerogenes*, determined by the serial dilution method in a glucose–peptone broth medium, were as follows:

Hydrochloride of:	Limiting dilution inhibiting growth after 24 hours. *Staph. aureus.*	*Aerobact. aerogenes.*
3-Amino-7 : 12-dihydroxycholanic acid	1 : 4,000	1 : 4,000
Methyl 3-amino-7 : 12-dihydroxycholanate	1 : 4,000	1 : 4,000
*iso*Amyl 3-amino-7 : 12-dihydroxycholanate	1 : 512,000	1 : 64,000
3-Amino-12-hydroxycholanic acid	1 : 16,000	1 : 8,000
*iso*Amyl 3-amino-12-hydroxycholanate	1 : 32,000	1 : 16,000

Experimental.

(A) *Oxidation of Methyl* 3 : 7 : 12-*Trihydroxycholanate* (*Methyl Cholate*) *with Oppenauer's Reagent.*—A solution of dry methyl cholate (30 g.) and aluminium *tert.*-butoxide (36 g.) in a mixture of dry benzene (900 c.c.) and dry acetone (375 c.c.) was boiled under reflux for 18 hours. The turbid reaction product was cooled and poured with stirring into 2N-sulphuric acid (600 c.c.). The benzene layer was separated and washed with 2N-sulphuric acid (twice), water (twice), sodium hydrogen carbonate solution (twice), and again with water. After drying (Na_2SO_4), the solvent was removed under reduced pressure, and the residue recrystallised from benzene–light petroleum (1 : 1). After recrystallisation from aqueous methyl alcohol, the methyl 7 : 12-dihydroxy-3-ketocholanate (18·7 g.) formed small prisms, m. p. 166°. From methyl alcohol it separated as large colourless prisms, m. p. 171—172°, $[\alpha]_D^{15}$ +36·5° in methyl alcohol (*c*, 2·5) (Found: C, 71·4; H, 9·6. Calc. for $C_{25}H_{40}O_5$: C, 71·4; H, 9·5%). There was no depression of m. p. in admixture with a specimen, m. p. 172—172·5°, $[\alpha]_D^{20}$ +36·1° in methyl alcohol (*c*, 1·0), prepared by Haslewood's method (*Biochem. J.*, 1944, **38**, 108).

The sodium hydrogen carbonate extract of the benzene solution (see above) was acidified with dilute sulphuric acid, and the resulting precipitate filtered off after 18 hours. The dried solid (1·5 g.) was extracted with light petroleum, and the residue crystallised from acetone–light petroleum. The product separated as short white needles (0·75 g.), m. p. 182—184° (sintering at 118—123°). After recrystallisation from aqueous alcohol, the product had m. p. 186—188°, $[\alpha]_D^{20}$ +36·9° in ethyl alcohol (*c*, 1·0) [cf. 7 : 12-dihydroxy-3-ketocholanic acid: m. p. 123°, $[\alpha]_D^{16}$ +37·5° (*c*, 3·7) in ethyl alcohol] (Found: C, 71·4; H, 9·3. Calc. for $C_{24}H_{38}O_5$: C, 70·9; H, 9·4%).

The Hammarsten reaction (see Haslewood, *Biochem. J.*, 1946, **40**, 52) of this compound was identical with that of 7 : 12-dihydroxy-3-ketocholanic acid (*i.e.*, yellow–green–violet) and different from that of both 3 : 12-dihydroxy-7-ketocholanic acid and 3 : 7-dihydroxy-12-ketocholanic acid.

Methyl 12-*Hydroxy*-3-*keto*-7-*acetoxycholanate.*—A solution of methyl 7 : 12-dihydroxy-3-ketocholanate (0·55 g.) in glacial acetic acid (5·5 c.c.) and acetyl chloride (0·42 g.) was kept at room temperature for 3 days and then poured with stirring into water (100 c.c.). The precipitated solid was collected after 15 minutes, washed with water, and crystallised from aqueous methyl alcohol. Recrystallisation from methyl alcohol gave *methyl* 12-*hydroxy*-3-*keto*-7-*acetoxycholanate* (0·4 g.) as colourless needles (Found: C, 70·1; H, 8·75. $C_{27}H_{42}O_6$ requires C, 70·1; H, 9·1%), $[\alpha]_D^{17}$ +59·4° in chloroform (*c*, 1·0), m. p. 193—195° alone and in admixture with a specimen of methyl 12-hydroxy-3-keto-7-acetoxycholanate {m. p. 193–195°, $[\alpha]_D^{17}$ +59·3° in chloroform (*c*, 2·5)} prepared from methyl 7 : 12-dihydroxy-3-ketocholanate obtained by Haslewood's method. The ester reacted with 2 equivs. of sodium hydroxide (0·1354 g. required 5·65 c.c. of 0·103N-sodium hydroxide for hydrolysis. $C_{27}H_{42}O_6$ requires 5·69 c.c.).

Methyl 3-*Keto*-7 : 12-*diacetoxycholanate.*—A solution of methyl 7 : 12-dihydroxy-3-ketocholanate (1·0 g.) in dry pyridine (4·0 c.c.) and acetic anhydride (3 c.c.) was heated at 100° for 30 hours. After cooling, the product was poured with stirring into cold water (200 c.c.), and the solid which separated was collected after 15 minutes, washed with water, and dissolved in ether (50 c.c.). The ethereal solution was washed with dilute hydrochloric acid (twice), water (twice), sodium hydrogen carbonate solution (twice), and again with water. After drying ($CaCl_2$), the solution was evaporated, and the residue crystallised from ethyl alcohol. A further crystallisation from aqueous ethyl alcohol gave methyl 7 : 12-diacetoxy-3-ketocholanate (0·6 g.) as fine needles, m. p. 186—189° (Found: C, 68·7; H, 8·8. Calc. for $C_{29}H_{44}O_7$: C, 69·0; H, 8·8%). After recrystallisation from benzene–light petroleum (1 : 1) it had m. p. 190—191°, $[\alpha]_D^{15}$ +56·8° in chloroform (*c*, 3·3). The m. p. was not depressed on admixture with an authentic specimen of methyl 7 : 12-diacetoxy-3-ketocholanate, m. p. 190—191°, $[\alpha]_D^{15}$ +57·3° in chloroform (*c*, 3·3).

Ethyl 7 : 12-*Dihydroxy*-3-*ketocholanate.*—A solution of methyl 7 : 12-dihydroxy-3-ketocholanate (1·5 g.) in ethyl alcohol (45 c.c.) containing concentrated sulphuric acid (1·0 c.c.) was boiled under reflux for 6 hours, cooled, and poured with stirring into water (30 c.c.). After 24 hours the precipitated solid was filtered off, washed with water, and crystallised from aqueous ethyl alcohol. Ethyl 7 : 12-dihydroxy-3-ketocholanate (1·1 g.) separated as fine colourless needles, m. p. 168—169°, and after recrystallisation from benzene containing a little light petroleum it (Found: C, 71·45; H, 9·85. Calc. for $C_{26}H_{42}O_5$: C, 71·85; H, 9·7%) had $[\alpha]_D^{16}$ +32·0° in chloroform (*c*, 4·8), m. p. 179—181° alone or in admixture with an authentic specimen of m. p. 179—181°, $[\alpha]_D^{16}$ +31·6° in chloroform (*c*, 4·0), prepared according to Haslewood's method (*loc. cit.*).

7 : 12-*Dihydroxy*-3-*ketocholanic Acid.*—The foregoing methyl ester (1·4 g.) was hydrolysed by boiling it for 4 hours under reflux with 0·96N-sodium hydroxide (15 c.c.) in ethyl alcohol (20 c.c.). The solution was then diluted with water (50 c.c.) and concentrated under reduced pressure to remove ethyl alcohol. After cooling, the solution was further diluted with water (50 c.c.) and acidified with dilute hydrochloric acid. After 16 hours the partly crystalline product which separated was filtered off, washed with water, and crystallised from aqueous ethyl alcohol. The dry compound was washed with ether–light petroleum (1 : 1) and recrystallised from aqueous ethyl alcohol. This afforded 7 : 12-*dihydroxy*-3-*ketocholanic acid* (0·8 g.) (Found: C, 68·7; H, 9·7; OEt, 9·8. $C_{24}H_{38}O_5.C_2H_5{\cdot}OH$ requires C, 69·0; H, 9·8; OEt, 9·95%) as tetrahedra, $[\alpha]_D^{16}$ +37·9° in ethyl alcohol (*c*, 4·0), m. p. 121—123° (cf. Sihn, *J. Biochem. Japan*, 1938, **27**, 425) alone or in admixture with an authentic specimen which had $[\alpha]_D^{16}$ +37·5° in ethyl alcohol (*c*, 3·7), m. p. 121—123°.

In order to prove that the ethoxyl content of the crystals (m. p. 121—123°) was due to solvation the following experiment was carried out. The crystals were heated *in vacuo* at 140° for 2 hours, and an ethoxyl determination was carried out on the glassy residue (Found: OEt, nil). When a portion of this glassy residue was crystallised from aqueous alcohol as before, crystals separated, m. p. 120—122° alone or in admixture with the original crystals. Crystallisation of the residue from a large volume of aqueous alcohol gave fine needles, m. p. 181—182° (cf. Kuwada and Morimoto, *loc. cit.*), which, when recrystallised from a small volume of aqueous alcohol, formed tetrahedra which first melted at 120°, then resolidified at 130—140°, and finally melted at 181—182°.

3-*Keto*-7 : 12-*diformoxycholanic Acid.*—A mixture of 7 : 12-dihydroxy-3-ketocholanic acid (0·45 g.),

sodium formate (0·15 g.), and formic acid (1·5 c.c.) was heated to 70—80° for 5 hours. The cooled solution was poured into water (100 c.c.), and the resulting precipitate collected after 1 hour, washed with water, dried *in vacuo* over phosphoric oxide, and crystallised from aqueous alcohol. The product (0·33 g.) separated as small white needles (m. p. 170° with previous sintering at 155°) which showed $[\alpha]_D^{18}$ +83·6° in ethyl alcohol (*c*, 1·0) (Found: C, 67·2; H, 8·1. $C_{26}H_{38}O_7$ requires C, 67·5; H, 8·3%). The *diformoxy*-compound was deformylated at room temperature with dilute aqueous sodium hydroxide (0·1377 g. required 6·60 c.c. of 0·1297N-sodium hydroxide. 7 : 12-Diformoxy-3-ketocholanic acid requires 6·87 c.c. for removal of the formyl groups and neutralisation of the carboxyl group). The deformylated product which separated upon acidification was filtered off, washed with water, and crystallised from aqueous ethyl alcohol. It separated as white needles, m. p. 190—192°. Thus, formylation and deformylation of the acid appear to effect its purification.

Oxime of 7 : 12-*Dihydroxy*-3-*ketocholanic Acid.*—A solution of the acid (10 g.) in the minimum of absolute alcohol was boiled under reflux for 3 hours with hydroxylamine hydrochloride (5 g.) and aqueous 5N-sodium hydroxide (12 c.c.). The cooled mixture was acidified with glacial acetic acid, poured into water (600 c.c.), and set aside for 18 hours. The resulting precipitate was collected, dried, and dissolved by prolonged boiling with absolute ethyl alcohol (250 c.c.). On cooling, small white prisms of the *oxime* separated (6·3 g.), m. p. 232° (decomp.), $[\alpha]_D^{21}$ +51·2° in ethyl alcohol (*c*, 1·0) (Found: C, 69·0; H, 9·4; N, 3·5. $C_{24}H_{39}O_5N$ requires C, 68·4; H, 9·3; N, 3·3%). A further 1·2 g. of oxime were recovered from the mother-liquors upon concentration.

The oxime formed from the acid fraction, m. p. 186—188° (0·1 g.), in the above manner showed $[\alpha]_D^{15}$ +52° in ethyl alcohol (*c*, 0·8) and m. p. 235° (decomp.).

3-*Amino*-7 : 12-*dihydroxycholanic Acid Hydrochloride.*—A solution of the oxime (7·5 g.) in boiling amyl alcohol (375 c.c.) was treated with sodium (30 g.), added in small pieces during 4·5 hours. The cooled solution was neutralised with dilute hydrochloric acid and evaporated under reduced pressure. The last traces of amyl alcohol were removed by simultaneous addition and distillation of water under reduced pressure. The residue was dissolved in 5N-sodium hydroxide, and the alkaline solution acidified with dilute hydrochloric acid, saturated with sodium chloride, and kept for 18 hours. The resulting precipitate was filtered off, dried *in vacuo* over phosphoric oxide, and dissolved in absolute alcohol (50 c.c.). The alcoholic solution was filtered, and evaporated to dryness. The resulting light-brown syrup upon crystallisation from alcohol and acetone (1 : 4) yielded 3-*amino*-7 : 12-*dihydroxycholanic acid hydrochloride* (4 g.) as small white needles. After recrystallisation from alcohol and acetone it showed m. p. 255° (decomp.), $[\alpha]_D^{25}$ +35·6° in ethyl alcohol (*c*, 1·0) (Found: C, 62·0; H, 9·55; N, 3·45; Cl, 8·5; H_2O, 3·8. $C_{24}H_{42}O_4NCl,H_2O$ requires C, 62·4; H, 9·5; N, 3·2; Cl, 8·0; H_2O, 3·9%).

Methyl ester. A solution of the above amino-acid hydrochloride (0·5 g.) in 1% methanolic hydrogen chloride (10 c.c.) was boiled under reflux for 3 hours. The solution was evaporated under reduced pressure and kept *in vacuo* over solid sodium hydroxide for 24 hours. Two crystallisations of the residue from alcohol and acetone (1 : 4) yielded the *methyl* ester *hydrochloride* (0·4 g.), m. p. 274° (decomp.), $[\alpha]_D^{18}$ +35·9° in ethyl alcohol (*c*, 1·0) (Found: N, 3·15; OMe, 6·4. $C_{25}H_{44}O_4NCl$ requires N, 3·0; OMe, 6·8%).

iso*Amyl ester.* A mixture of 3-amino-7 : 12-dihydroxycholanic acid hydrochloride (0·5 g.), *iso*amyl alcohol (30 c.c.), and 10N-hydrochloric acid (2 c.c.) was heated on a steam-bath for 3 hours. The solvents were removed by distillation under reduced pressure, and the residue crystallised from alcohol and acetone. The iso*amyl* ester *hydrochloride* thus obtained (0·45 g.), on drying *in vacuo* over phosphoric oxide and sodium hydroxide, had m. p. 260° (decomp.), $[\alpha]_D^{25}$ +29·7° in ethyl alcohol (*c*, 1·0) (Found: C, 66·75; H, 10·0; N, 2·7; Cl, 7·4; H_2O, 1·9. $C_{29}H_{52}O_4NCl,\frac{1}{2}H_2O$ requires C, 66·6; H, 10·2; N, 2·7; Cl, 6·9; H_2O, 1·72%).

(B) *Oxidation of Methyl Deoxycholate with Aluminium* tert.-*Butoxide.*—A solution of methyl deoxycholate (14·7 g.) and aluminium *tert.*-butoxide (15·5 g.) in a mixture of dry benzene (400 c.c.) and dry acetone (160 c.c.) was boiled for 18 hours under reflux. The solution was cooled and poured with stirring into 2N-sulphuric acid (500 c.c.). The benzene layer was separated, washed with 2N-sulphuric acid (twice), sodium hydrogen carbonate (twice), and water (once). After drying ($CaCl_2$), the solution was evaporated to give a pale yellow syrup which readily crystallised. Recrystallisation from aqueous ethyl alcohol gave material, m. p. 134—138°. Further crystallisation of this product from light petroleum afforded methyl 12-hydroxy-3-ketocholanate (8·3 g., 57%), m. p. 140—142°, $[\alpha]_D^{23}$ +51° in ethyl alcohol (*c*, 0·5) (Found: C, 74·25; H, 10·05. Calc. for $C_{25}H_{40}O_4$: C, 74·2; H, 10·0%).

The sodium hydrogen carbonate extract of the benzene solution was acidified with dilute sulphuric acid, and the resulting precipitate collected after 18 hours, washed with water, and dried. Crystallisation of the crude solid (2·3 g.) from aqueous acetic acid yielded white plates (1·8 g.), m. p. 105—110°. Recrystallisation from acetone and light petroleum yielded 12-hydroxy-3-ketocholanic acid, $[\alpha]_D^{18}$ ++51° in ethyl alcohol (*c*, 1·0), m. p. and mixed m. p. 155—158°. The compound was converted into its oxime (see below), m. p. 143—144°, $[\alpha]_D^{21}$ +60·6° in ethyl alcohol (*c*, 1·0), in the usual way.

12-*Hydroxy*-3-*ketocholanic Acid.*—A solution of methyl 12-hydroxy-3-ketocholanate (1·3 g.) in absolute alcohol (20 c.c.) and 30% sodium hydroxide (2·5 c.c.) was kept at room temperature for 20 hours, poured into water (600 c.c.), and acidified, and the resulting precipitate was filtered off and washed with water. Crystallisation from dilute acetic acid gave a product, m. p. 105°. Recrystallisation from aqueous alcohol yielded 12-hydroxy-3-ketocholanic acid (1·05 g.), m. p. 156—158°, $[\alpha]_D^{18}$ +52° in ethyl alcohol (*c*, 1·0).

Oxime. A mixture of this acid (0·95 g.), absolute alcohol (4 c.c.), hydroxylamine hydrochloride (0·5 g.), and 5N-sodium hydroxide (2 c.c.) was boiled under reflux for 3 hours. The cooled solution was acidified with glacial acetic acid, poured into water, and kept for 18 hours. The resulting crystalline solid was filtered off, washed, dried *in vacuo* over phosphoric oxide, and recrystallised first from absolute alcohol and then from aqueous methyl alcohol. The *oxime* (0·8 g.) had m. p. 144—145°, $[\alpha]_D^{21}$ +60·9° in ethyl alcohol (*c*, 1·0) (Found: C, 67·95; H, 9·6; N, 3·4; H_2O, 4·2. $C_{24}H_{39}O_4N,H_2O$ requires C, 68·0; H, 9·75; N, 3·3; H_2O, 4·25%).

Reduction of the Oxime of 12-*Hydroxy*-3-*ketocholanic Acid.*—A solution of the oxime (1 g.) in boiling

amyl alcohol (50 c.c.) was treated with sodium (5 g.) added portionwise during 4—5 hours. The cooled solution was neutralised with dilute hydrochloric acid and evaporated to dryness under reduced pressure. The residue was dissolved in 2N-sodium hydroxide, acidified with 2N-hydrochloric acid, saturated with sodium chloride, and set aside for 18 hours. The resulting precipitate was filtered off, dried *in vacuo* over phosphoric oxide, and dissolved in absolute alcohol. The alcoholic solution was filtered, the filtrate concentrated to dryness, and the residue crystallised from alcohol–acetone. Recrystallisation from alcohol–acetone gave 3-*amino*-12-*hydroxycholanic acid hydrochloride* (0·25 g.), $[\alpha]_D^{21}$ +50·8° in ethyl alcohol (*c*, 1·0), m. p. 239° (sintering at 185°) (Found, after drying at 200°: C, 67·3; H, 9·8; N, 3·4. $C_{24}H_{43}O_3NCl$ requires C, 67·3; H, 9·9; N, 3·3%).

The residue from the mother-liquors of the first crystallisation was dissolved in dilute aqueous sodium hydroxide, and the slightly cloudy solution extracted with ether. The aqueous solution was acidified with dilute hydrochloric acid, and the resulting precipitate filtered off. Crystallisation from aqueous acetone yielded slightly coloured needles, m. p. 175—180° (0·1 g.). The compound was dissolved in aqueous alcohol, and the solution treated with charcoal, filtered, and allowed to crystallise. The white needles thus produced had m. p. 175—180°, raised by further crystallisation from aqueous methyl alcohol to 180—182°. This product, which did not contain nitrogen, was not investigated further.

iso*Amyl* 3-*Amino*-12-*hydroxycholanate Hydrochloride*.—A solution of 3-amino-12-hydroxycholanic acid hydrochloride (0·1 g.) in *iso*amyl alcohol (6 c.c.) and 10N-hydrochloric acid (0·4 c.c.) was heated on a steam-bath for 6 hours. The solution was evaporated to dryness under reduced pressure, and the residue crystallised from alcohol–acetone. The iso*amyl* ester *hydrochloride* separated as white prisms, m. p. 242—245° (decomp.), $[\alpha]_D^{18}$ +35·3° in ethyl alcohol (*c*, 1·0) (Found: N, 2·7. $C_{29}H_{52}O_3NCl$ requires N, 2·8%).

Treatment of 3-*Chloro*-7 : 12-*dihydroxycholanic Acid with Ammonia*.—A suspension of 3-chloro-7 : 12-dihydroxycholanic acid (1·2 g.; Wieland, Honold, and Pascual-Vila, *loc. cit.*) in alcoholic ammonia (15 c.c.) containing ammonium iodide (0·3 g.) was heated at 180° for 8 hours. The product was extracted with ethyl alcohol, and the combined extracts evaporated under reduced pressure. The residual solid was suspended in hot water (25 c.c.), and N-sodium hydroxide added to complete dissolution (ammonia evolved). Separation of the sodium salt of an unsaturated acid occurred on cooling the solution. The solid was collected at the pump, and the filtrate acidified with acetic acid; the precipitate thus formed was filtered off, washed with water, and dried. The filtrate was free from bile acid derivatives. Recrystallisation of the product (0·5 g.) from ethyl acetate and from ethyl alcohol gave small prisms, m. p. 214—215°. The product was unsaturated, decolorised a solution of bromine in carbon tetrachloride, and did not contain nitrogen. It appeared to be 7 : 12-dihydroxy-Δ^3-cholenic acid, m. p. 215—217° (Wieland, Honold, and Pascual-Vila, *loc. cit.*), in admixture with which it gave no depression of the m.p. It was noted that the unsaturated acid of Wieland *et al.* (*loc. cit.*) formed a sparingly soluble sodium salt.

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462. *Aromatic Hydrocarbons. Part LII. Naphtho*(2′ : 3′ : 1 : 2)-*pyrene*, 1 : 2-4 : 5-8 : 9-*Tribenzpyrene, and a New Synthesis of* 1 : 2-3 : 4-*Dibenzanthracene.*

By E. CLAR.

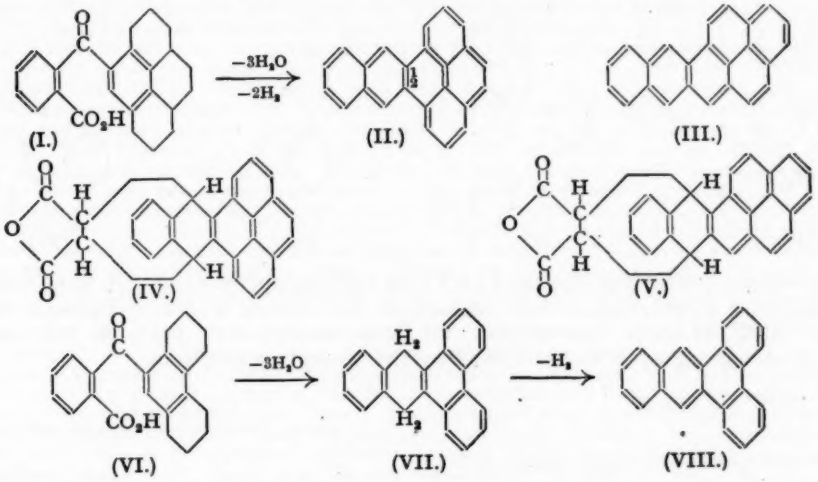
Decahydropyrene was condensed with phthalic anhydride. The keto-acid so formed was fused with sodium chloride and zinc chloride and dehydrogenated with copper powder to naphtho(2′ : 3′-1 : 2)pyrene. In the same way 1 : 2-3 : 4-dibenzanthracene was obtained from *o*-octahydrophenanthroylbenzoic acid.

Octahydroanthracene reacted with two molecules of benzyl chloride and aluminium chloride to form 9 : 10-dibenzyl-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydroanthracene, which on dehydrogenation with copper yielded 1 : 2-4 : 5-8 : 9-tribenzpyrene, with 2 : 3-8 : 9-dibenzperylene as a by-product.

DECAHYDROPYRENE reacts in the Friedel–Crafts reaction as an alkylated benzene (Clar, *Chem. Ber.*, 1948, **81**, 520). With phthalic anhydride the *acid* (I) was thus obtained in good yield. When (I) was melted with a mixture of sodium chloride and zinc chloride at 330°, water was easily split off, and the partly hydrogenated hydrocarbon gave, on heating with copper powder, *naphtho*(2′ : 3′-1 : 2)*pyrene* (II). This pale yellow naphthopyrene (II) is strikingly different from the isomeric deep-orange-yellow naphtho(2′ : 3′-3 : 4)pyrene (III) (Cook and Hewett, *J.*, 1933, 403; Clar, *Ber.*, 1936, **69**, 1684). The absorption spectra of the two hydrocarbons are shown in Fig. 1; that of (III) resembles rather that of 1 : 2-6 : 7-dibenzpyrene (Clar, *Ber.*, 1943, **76**, 609).

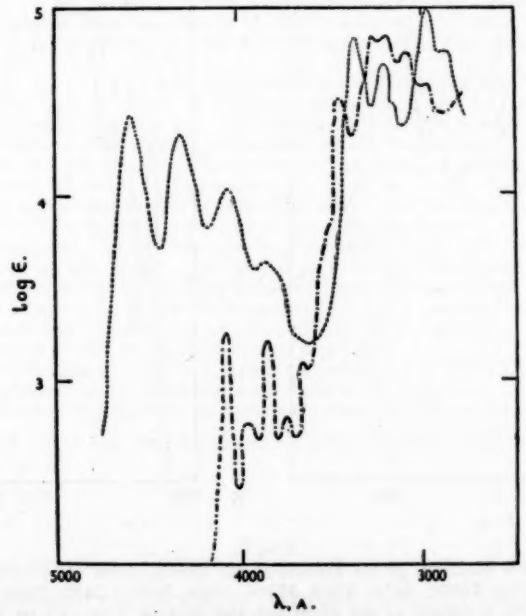
However, the differences almost disappear in the *addition products* (IV and V) with maleic anhydride. The absorption spectra of these two compounds, shown in Fig. 2, are typical pyrene spectra and differ not more than those of isomeric alkyl derivatives.

The new method of ring closure of *o*-polyhydroaroylbenzoic acids with sodium chloride and zinc chloride can be successfully applied to other cases, *e.g.*, to *o*-octahydro-9-phenanthroyl-



benzoic acid (VI). This acid is easily obtained from phthalic anhydride, octahydrophenanthrene, and aluminium chloride (Barnett and Lawrence, *J.*, 1935, 1104). Dehydration

FIG. 1.



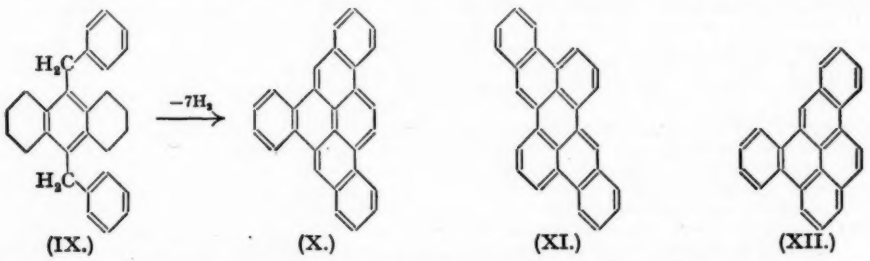
—·—·—·— *Absorption spectrum of naphtho*(2′ : 3′-1 : 2)*pyrene* (*II*) *in benzene. Band maxima in* A. : 4075, 3960, 3860, 3750, 3670; 3450; 3280; 3210; 3090, 2970.

..... *Absorption spectrum of naphtho*(2′ : 3′-3 : 4)*pyrene* (*III*) *in benzene. Band maxima in* A. : 4580, 4310, 4060, 3850; 3350, 3200; 2970, 2860.

by melting with sodium chloride and zinc chloride gave a mixture of 1 : 2-3 : 4-dibenzanthracene (VIII) and its 9 : 10-dihydro-derivative (VII), which could be separated by means of the dissociable maleic anhydride addition product of (VIII). Dehydrogenation of the crude mixture of (VII) and (VIII) with copper powder gave (VIII).

Octahydroanthracene reacted with two molecules of benzyl chloride in presence of a

catalytic amount of aluminium chloride to form 9 : 10-dibenzyl-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydroanthracene (IX), which with copper powder at 400—420° yielded, by dehydrogenation



(IX.) (X.) (XI.) (XII.)

and simultaneous double ring closure, 1 : 2-4 : 5-8 : 9-tribenzpyrene (X). In some experiments this product was mixed with a small amount of the isomeric 2 : 3-8 : 9-dibenzperylene (XI) (Clar, *Ber.*, 1932, **65**, 846; Schauenstein and Bürgermeister, *Ber.*, 1943, **76**, 208), which was isolated by chromatography and identified by the absorption spectrum.

FIG. 3.

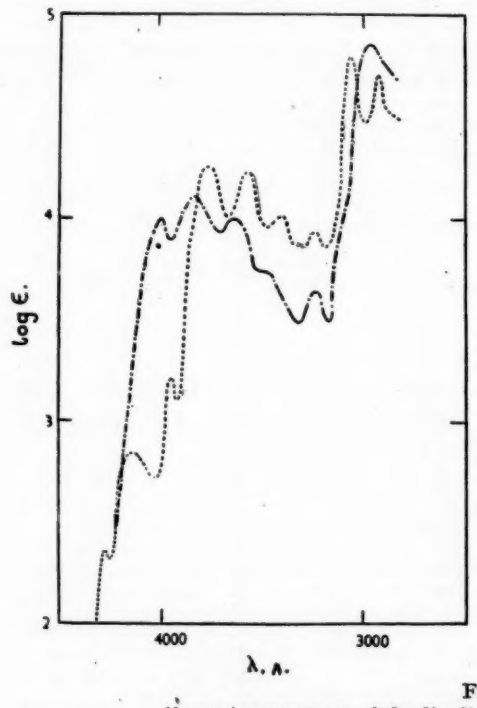


FIG. 2.

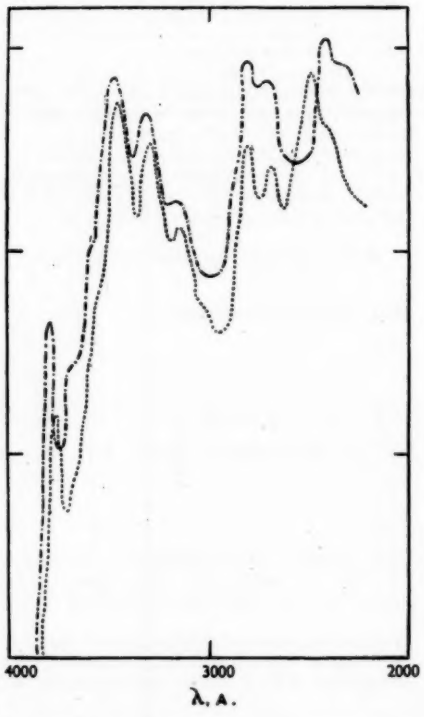


FIG. 2.

— · — · — · — *Absorption spectrum of the disodium salt derived from (IV) in water. Band maxima in* A.: 3770, 3690; 3470, 3305, 3170; 2805, 2695; 2430, 2360.

..... *Absorption spectrum of the disodium salt derived from (V) in water. Band maxima in* A.: 3755, 3660; 3440, 3280, 3145; 2805, 2690; 2510, 2400.

FIG. 3.

— · — · — · — *Absorption spectrum of* 1 : 2-4 : 5-8 : 9-*tribenzpyrene* (*X*) *in benzene. Band maxima in* A.: 3990; 3820, 3640, 3470; 3220; 2950.

..... *Absorption spectrum of* 1 : 2-4 : 5-*dibenzpyrene* (*XII*) *in benzene. Band maxima in* A: 4160, 3960; 3780, 3600, 3430, 3275; 3065, 2945.

The absorption spectrum of 1 : 2-4 : 5-8 : 9-tribenzpyrene (X) shows considerable differences from that of pyrene and is related to the structurally similar 1 : 2-4 : 5-dibenzpyrene (XII) (Fig. 3) (Clar, *Ber.*, 1943, **76**, 613).

EXPERIMENTAL.

1-o-*Carboxybenzoyldecahydropyrene* (I).—Powdered aluminium chloride (150 g.) was gradually added to a mixture of decahydropyrene (106 g.) and phthalic anhydride (75 g.) in benzene (200 c.c.). After agitation for 2 hours at room temperature, the mixture was decomposed with dilute hydrochloric acid and ice. The benzene was removed by steam-distillation, and the residue was dissolved in dilute sodium hydroxide solution. The hot filtered solution was acidified with hydrochloric acid. The precipitated acid crystallised immediately when touched with a few drops of ether. Recrystallisation from dilute acetic acid gave colourless prisms, which melted at 176—178° (uncorr.) and dissolved in sulphuric acid to give a yellowish-brown solution (Found: C, 79·6; H, 6·5. $C_{24}H_{24}O_3$ requires C, 80·0; H, 6·7%).

Naphtho(2′ : 3′-1 : 2)*pyrene* (II).—The acid (I) (95 g.) was mixed with sodium chloride (10 g.) and zinc chloride (50 g.) and heated to 330°. The green colour of the melt disappeared during a vigorous evolution of steam, and two layers were formed. The upper layer was dissolved in hot xylene and filtered, and the xylene evaporated. Copper powder (8 g.) was added and the molten hydrocarbon was heated at 400—410° for 2 hours. Hydrogen was evolved. The powdered residue of *naphthopyrene* was sublimed in a vacuum at 300° and then recrystallised from xylene, yielding long pale yellow needles, m. p. 259—260° (evacuated capillary; uncorr.) (Found: C, 95·2, 95·3; H, 4·6, 4·7. $C_{24}H_{14}$ requires C, 95·3; H, 4·7%), which gave a reddish-brown solution in concentrated sulphuric acid. The solution in organic solvents showed a strong blue fluorescence. A *picrate*, forming long red needles, m. p. 212—213° (decomp.; evacuated capillary; uncorr.) (Found: N, 8·4. $C_{30}H_{17}O_7N_3$ requires N, 7·9%), was obtained by use of an excess of picric acid in hot benzene.

1′ : 4′-endo*Ethylenenaphtho*(2′ : 3′-1 : 2)*pyrene-αβ-dicarboxylic Anhydride* (IV).—The naphthopyrene (II) (1 g.), maleic anhydride (1 g.), and xylene (20 c.c.) were boiled for 1 hour. Dilute sodium hydroxide was added and the xylene removed with steam. The filtered hot solution was acidified with hydrochloric acid. The precipitated *anhydride*, when recrystallised from acetic anhydride, formed colourless needles, m. p. 238—245° (decomp.; evacuated capillary; uncorr.), which gave a yellowish-green solution in concentrated sulphuric acid, which later became bluish-green (Found: C, 84·1; H, 3·8. $C_{28}H_{16}O_3$ requires C, 84·0; H, 4·0%).

1 : 2-3 : 4-*Dibenzanthracene* (VIII).—*o*-Octahydro-9-phenanthroylbenzoic acid (VI) was fused with sodium chloride and zinc chloride as described for preparation of (I) and distilled directly from the melt in a vacuum. The distillate consisted of 1 : 2-3 : 4-dibenzanthracene (VIII) and its dihydro-derivative (VII), which can be separated through the addition product of (VIII) with maleic anhydride (Clar and Lombardi, *Ber.*, 1932, **65**, 1418). If only 1 : 2-3 : 4-dibenzanthracene is desired, the crude dehydration product is dehydrogenated as described above. 1 : 2-3 : 4-Dibenzanthracene formed long colourless needles, m. p. 205°(uncorr.), identical, by direct comparison, with an authentic sample (Clar, *Ber.*, 1929, **62**, 350, 1574).

9 : 10-*Dibenzyl*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydroanthracene* (IX).—Benzyl chloride (126 g.) was added dropwise to an agitated mixture of octahydroanthracene (90 g.) and powdered aluminium chloride (5 g.) in tetrachloroethane (100 c.c.). Colourless crystals separated, and hydrochloric acid was evolved. After decomposition with dilute hydrochloric acid the solvent was removed with steam. The residue was dissolved in hot xylene. The *product* crystallised in colourless needles (39 g.), m. p. 189—190° (Found: C, 92·0; H, 8·2. $C_{28}H_{30}$ requires C, 91·8; H, 8·2%), from the solution on cooling. It gave a brown solution in hot concentrated sulphuric acid. The mother-liquor still contained much of the hydrocarbon, part of which could be obtained by concentration.

1 : 2-4 : 5-8 : 9-*Tribenzpyrene* (X).—Dibenzyloctahydroanthracene (IX) was heated with 15% of copper powder for 4 hours at 400—420°. Hydrogen was evolved and some oil, formed by cracking, distilled. The residual *tribenzpyrene* gave, after sublimation in a vacuum and repeated recrystallisation from xylene, pale yellow leaflets, m. p. 297° (evacuated capillary; uncorr.), which gave an olive-green solution in warm concentrated sulphuric acid (Found: C, 95·5; H, 4·9. $C_{28}H_{16}$ requires C, 95·4; H, 4·6%). The fluorescence of the solution in xylene was blue.

In some cases the hydrocarbon contained a small quantity of 2 : 3-8 : 9-dibenzperylene which was identified by its absorption bands at 4340 and 4080 A. in benzene. It could be removed by chromatographic adsorption of the solution in benzene on an alumina column.

This work was carried out during the tenure of an I.C.I. Research Fellowship, for which I express my indebtedness.

UNIVERSITY OF GLASGOW. [*Received, March 7th*, 1949.]

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463. *Studies on the Nature of Chemisorptive Bonds. Part II. The Catalytic Toxicity of Organometallic Compounds.*

By E. B. MAXTED and K. L. MOON.

The apparent importance of *d*-shell filling in determining the capacity of a metallic derivative to form a strong chemisorptive bond to a platinum hydrogenation catalyst has been further examined by measurements of the toxicity of organometallic compounds in which *s* and *p* valency orbitals, of the next higher order to a filled *d* shell, are already occupied in covalent bonding with carbon, in place of being unoccupied as in the catalytically toxic metallic ions. The results confirm the inference that the *d* shell in toxic metals is involved in the bond to the catalyst.

It has been shown in Table I of Part I (this vol., p. 1987) that, in the case of the poisoning of a platinum hydrogenation catalyst by metallic ions, the capacity of a given ion to form a strong

chemisorptive bond—which is a characteristic of catalytic toxicity—seems to be dependent on a suitable electronic configuration in the *d* shell of the toxic ion immediately inside the ordinary valency orbitals, in that toxic properties are shown only by those ions which have all of the five *d* orbitals occupied either by electron pairs or at least by single electrons. If, on the other hand, any unoccupied *d* orbitals are present, or if no *d* orbitals are possible as in the ground states of the simpler elements, the power of forming a strong bond vanishes and the ion is accordingly non-toxic.

This apparently necessary condition for strong bonding has now been examined further with other metallic derivatives in order to obtain confirmatory evidence for the part played by *d* electrons in determining the observed toxicity. In the metallic ions themselves, unoccupied *s* and *p* orbitals (which have been left vacant by the loss of valency electrons and which are of the next higher order to that of the *d* band) also occur; and the possibility of some occupation of these vacant levels—for instance, by a relatively small excitation—by electrons, which might then take part in chemisorptive bond formation and thus obscure any inference that the strong poison bond is really due to a suitable *d*-shell occupation, cannot accordingly be entirely ruled out so long as these vacant *s* and *p* orbitals are present.

For this reason it has been considered of interest to carry out toxicity tests with metallic compounds in which the *s* and *p* bands, in place of being vacant as in the metallic ions, are already involved in bond formation with another element. To this end the toxicity of the series, dimethylmercury, trimethylindium, and tetramethyl-lead towards a platinum catalyst has been examined, these substances being representative organometallic compounds containing respectively a bivalent, a tervalent, and a quadrivalent metal which is known to be toxic in the form of an ion. It may be noted that the generally accepted metal-to-carbon bond structure in these organometallic compounds involves, on the part of the metal, two mutually equivalent *sp* hybrid orbitals for mercury, three sp^2 orbitals for indium, and four hybridised tetrahedral sp^3 orbitals for lead, each of these orbitals giving, by covalent bonding to carbon, a condition equivalent to electronic saturation in *s* and *p* levels of the metal. Especially in the case of tetramethyl-lead, with all four of its *s* and *p* orbitals already taken up in bond formation with carbon, *i.e.*

it will be seen that any toxicity which may be observed would seem to make quite clear the importance of the part played by the filled *d* band of the metal in the formation of the strong chemisorptive bond to a platinum catalyst.

As with the toxic metallic ions dealt with in Part I, it is desirable to establish the primary toxicity of the organometallic compounds as such. The evidence for strong adsorptive bonds such as would lead to the obstructive occupation of catalyst surface and consequently to catalytic toxicity follows from the degree of the observed adsorption even when the organometallic compounds are present only in extremely low concentrations; and that the seat of this strong adsorption lies in the unchanged organometallic compounds themselves can be shown by the reversibility of the adsorption indicated by the form of the adsorption isotherms, which are consistent with an adsorption–desorption equilibrium in which the organometallic compound is adsorbed and desorbed as such. Further, the limit set by this equilibrium for the degree of the removal of the compound from the free phase is not passed even on long storage in contact with platinum-black, at any rate at room temperature, as would be the case if the adsorbed compound gradually broke down into a deposit of the metal.

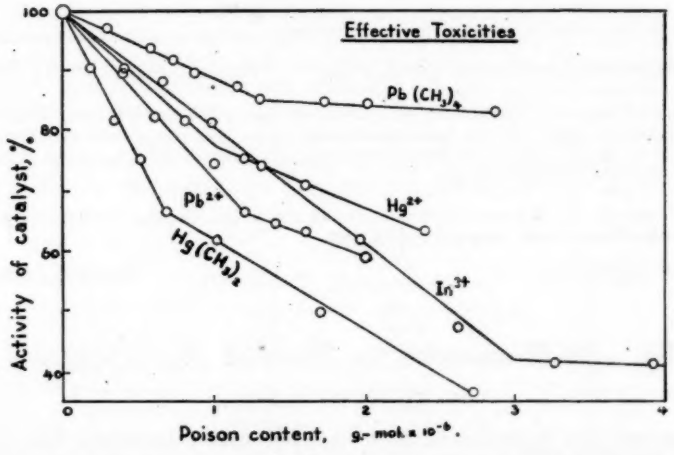
It is known that, at high temperatures and at high hydrogen pressures, organometallic compounds can be hydrogenated to the metal and a hydrocarbon in a somewhat similar way to the corresponding high-pressure reduction of metallic salt solutions. Thus Ipatiew, Rasuwajew, and Bogdanow (*Ber.*, 1930, **63**, 335) have shown that, in benzene solution, the decomposition of tetramethyl-lead begins to be detectable after 24 hours at temperatures above 125° with a hydrogen pressure of 60 atm.; but it is doubtful whether this is significant under the conditions of the present tests, which were carried out at 30° at atmospheric pressure: indeed, even if it could be shown that some preferential hydrogenation of the organometallic compound took place in spite of its vanishingly small concentration (which is of the order of one ten-thousandth of the molecular concentration of the *cyclo*hexene), this would in itself further emphasise the experimentally observed fact that these organometallic compounds must be very strongly adsorbed.

Experimental.

The toxicity of these organometallic compounds towards platinum was measured by the technique adopted in previous work on catalyst poisoning, namely, by following the inhibitive effect of a gradually increased quantity of the poison, in *cyclo*hexane solution, on the activity of a constant quantity of platinum black for the hydrogenation of *cyclo*hexene, the hydrogenation being carried out in a shaker, at 30°, under standardised conditions. The charge introduced into the hydrogenation pipette consisted in each case of 0·05 g. of stock platinum-black, 2 c.c. of *cyclo*hexene, and 8 c.c. of *cyclo*hexane including that added with the poison. The dimethylmercury and trimethylindium were supplied by the courtesy of Mr. G. E. Coates. The tetramethyl-lead was made by a slight modification of the method described by Jones and Werner (*J. Amer. Chem. Soc.*, 1918, **40**, 1273). Standard solutions of each of these were made up by dissolving known weights of the poisons in *cyclo*hexane, small quantities of these original solutions being further diluted with *cyclo*hexane to the very low concentrations used. With dimethylmercury and tetramethyl-lead no special precautions were necessary, save those against loss of poison by volatility and care in preparation by reason of their physiological toxicity; but rigid precautions against the access of traces of water or water vapour are necessary with trimethylindium on account of the ease with which this is attacked even by traces of moisture.

For dimethylmercury and tetramethyl-lead both effective and true toxicity curves were plotted, the latter involving the plotting of the poisoning effect against the amount of poison actually adsorbed on the catalyst, in place of against the total poison present in the system as in the effective toxicity graphs; and the toxicity of the organometallic compound was also compared with that of the metallic ion. With trimethylindium, on the other hand, on account of the ease with which it is destroyed, it was only found possible, even by working with freshly diluted solutions of the concentration required, to show that it is strongly toxic; but this toxicity towards platinum was definitely established.

Fig. 1.



The effective poisoning graphs obtained, which are of the usual flexed linear type, are summarised in Fig. 1. In the case of the metallic ions, the hydrogenation system used, including the solvent, was somewhat different from that taken for the organometallic compounds, since the metallic chlorides used as a source of mercury, indium, and lead ions are not soluble in *cyclo*hexane; and, for these, the system consisted of 0·05 g. of stock platinum-black, 5 c.c. of 2N-crotonic acid in alcohol, and 5 c.c. of water, including that added with the poison. It is known that mercuric chloride, particularly, is not easily ionised in aqueous solution; but a calculation on the basis of its dissociation constants showed that dissociation is substantially complete at the vanishingly small concentrations used in the poisoning tests.

As has already been mentioned, trimethylindium could not be stored sufficiently long in solution to enable a complete curve to be determined satisfactorily; but an indication of its high toxicity was obtained by introducing 0·005 g. of trimethylindium into a standard *cyclo*hexane–*cyclo*hexene charge taken from a stock which had been previously dried by treatment with, and distillation over, metallic sodium. Hydrogenation tests in the presence of 0·05 g. of platinum showed that this small quantity of trimethylindium was sufficient to poison the catalyst almost completely, the rate of hydrogen absorption being reduced from a value of 29·2 c.c. per minute in a blank run without the indium down to about 0·1 c.c. per minute in the presence of the indium compound.

For the determination of the true toxicity graphs for dimethylmercury and tetramethyl-lead, partition measurements in *cyclo*hexane solution were carried out in the usual way (*J.*, 1938, 2071) by allowing a solution of the poison to remain in contact with a charge of catalyst under similar conditions to those in the hydrogenation tests, *i.e.*, at 30° and with 0·05 g. of the platinum-black to each 10 c.c., the unadsorbed poison in the supernatant liquid being subsequently estimated catalytically. In agreement with the general results of earlier work, the adsorption of the poison was found to be an approximately linear function of the total poison concentration throughout the poison concentration range which had been used in the effective poisoning tests. The results of these partition tests for dimethylmercury and

tetramethyl-lead are given in Fig. 2, from which it will be seen that, in the effective toxicity tests, about 61% of the total dimethylmercury present, and about 71% of the tetramethyl-lead, were adsorbed on the 0·05 g. of platinum used. Accordingly, in order to convert the effective toxicity graphs for dimethylmercury and tetramethyl-lead into true toxicity graphs, it is necessary to multiply the bulk concentrations of poison by a factor of 0·61 and 0·71, respectively. Applying this correction, the true toxicity

FIG. 2.

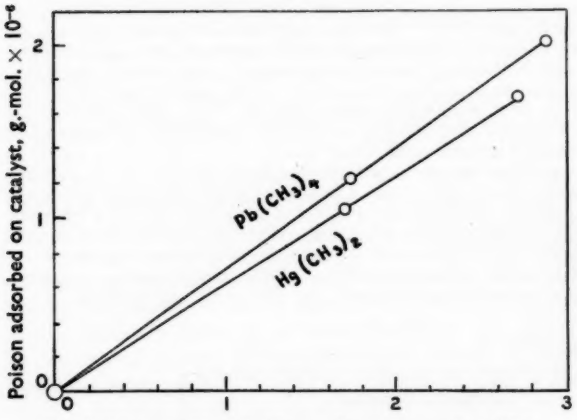
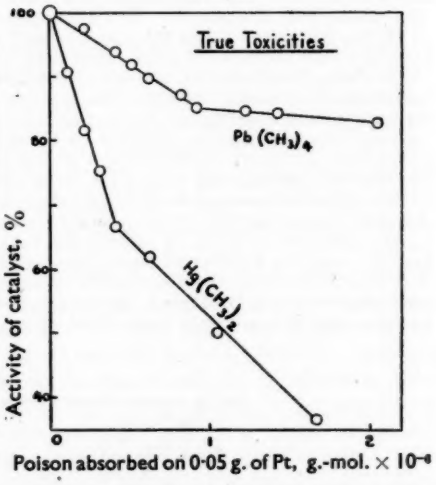


FIG. 3.



graphs are as given in Fig. 3. A point to be noticed is that tetramethyl-lead, although catalytically poisonous, is, contrary to expectations based on relative size, less toxic than dimethylmercury. This may be due to a steric factor, since the metal atom in the tetramethyl compound is probably shielded to some extent by the four methyl groups.

One of the authors (E. B. M.) expresses his thanks for a Leverhulme Research Fellowship for the carrying out of work of which this paper forms a part.

UNIVERSITY OF BRISTOL. [*Received, March 16th,* 1949.]

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464. cis-*Elimination in Thermal Decompositions.*

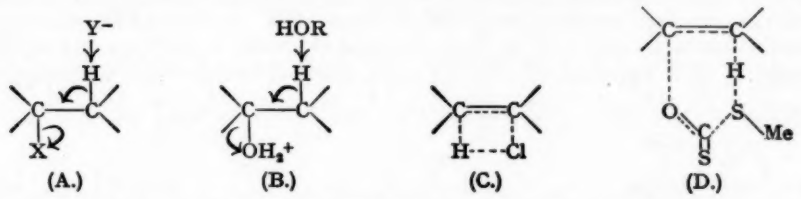
By D. H. R. BARTON.

It is emphasised that thermal elimination reactions of the unimolecular type must involve a four-centre planar transition state and that, as a consequence, such reactions must be stereochemically specific in requiring a *cis*-configuration of the eliminated groups. This generalisation is illustrated by reference to the thermal decompositions of methyl xanthates and of benzoates in the terpenoid and the steroid field respectively. It is suggested that the concept of *cis*-elimination in this type of reaction provides a useful method for the elucidation of stereochemical relationships. In particular, it confirms the assignment of configuration at the 7-position in steroids recently made by Fieser, Fieser, and Chakravarti (*J. Amer. Chem. Soc.*, 1949, **71**, 2226). Configurations are assigned to *iso*thujyl alcohol and to *neoiso*thujyl alcohol.

IT has long been recognised that addition to olefinic linkages by ionic mechanisms, in the absence of complicating factors, proceeds in the *trans*-sense. More recently the corresponding requirement of *trans*-elimination through heterolytic E_2 reaction mechanisms has become generally accepted (see Hughes, Ingold, *et al.*, *J.*, 1948, 2093). The transition state in reactions of this type is pictured as in (A), where X indicates the eliminated negative ion and Y the attacking nucleophilic reagent. From the stereochemical point of view this *trans*-type of ionic elimination has been very well illustrated by the acid-catalysed dehydrations of cyclic alcohols (see *inter al.*, Zeitschel and Schmidt, *Ber.*, 1926, **59**, 2298; Hückel *et al.*, *Annalen*, 1930, **477**, 99; Vavon and Barbier, *Bull. Soc. chim.*, 1931, **49**, 567; Price and Karabinos, *J. Amer. Chem. Soc.*, 1940, **62**, 1159). Presumably the transition state in reactions of this type is as illustrated in (B) where R is H or the alicyclic radical of the alcohol being dehydrated.

There is, however, another important type of elimination mechanism which is stereo-

chemically specific in the *cis*-sense, and which has not yet received adequate recognition. This mechanism is illustrated by those olefin-forming thermal decomposition reactions which occur



(A.) (B.) (C.) (D.)

homogeneously and are unimolecular.* Thus the pyrolyses of ethyl chloride, 1 : 1-dichloroethane, *iso*propyl chloride, and *tert.*-butyl chloride all proceed by the unimolecular mechanism giving hydrogen chloride and the corresponding olefin (Barton and Howlett, this vol., p. 165; Barton and Onyon, *Trans. Faraday Soc.*, 1949, **45**, 725; Barton and Head, forthcoming publication). The transition state in these reactions, shown in (C), is a specific example of the four-centre type of problem (compare Sherman, Quimby, and Sutherland, *J. Chem. Physics*, 1936, **4**, 732). It is a characteristic of the latter that the four centres must lie, suitably disposed with respect to each other, in one plane to ensure the minimisation of the activation energy (Glasstone, Laidler, and Eyring, " The Theory of Rate Processes," McGraw-Hill, 1941, p. 90) and, therefore, *cis*-stereochemistry *must* be demanded in the reactant. This deduction applies quite generally to unimolecular thermal decomposition reactions.

The most extensive evidence in this connection is provided by the experiments of Hückel, Tappe, and Legutke (*Annalen*, 1940, **543**, 191) on the stereochemical specificity of Tschugaeff's xanthate reaction. The latter is a process involving the thermal decomposition of the methyl xanthates of alcohols, suitably alicyclic alcohols, to give carbon oxysulphide, methanethiol and the corresponding olefin (Tschugaeff, *Ber.*, 1899, **32**, 3332; compare McAlpine, *J.*, 1932, 912); the transition state may be represented as in (D). The results are summarised in the table. Also included in this table are data for a number of other methyl xanthates, the

Methyl xanthate from :	Formula. *	Relation of OH to bridgehead H.	Elimination, %. Towards bridgehead.	Away from bridgehead.
(−)-Menthol	(I)	*cis*	~70	~30
(+)-*neo*Menthol	(II)	*trans*	~20	~80
trans-α-Decalol (m. p. 49°)	(III)	*trans*	~20	~80
trans-α-Decalol (m. p. 63°)	(IV)	*cis*	~80	~20
cis-α-Decalol (m. p. 93°)	(V)	*trans*	~10	~90
(−)-Pinocampheol	(VI)	*trans*	—	Main product
(−)-*neo*Thujyl alcohol	(VII)	*trans*	—	Main product
(+)-*iso*Thujyl alcohol	(VIII)	*cis*	Main product	—

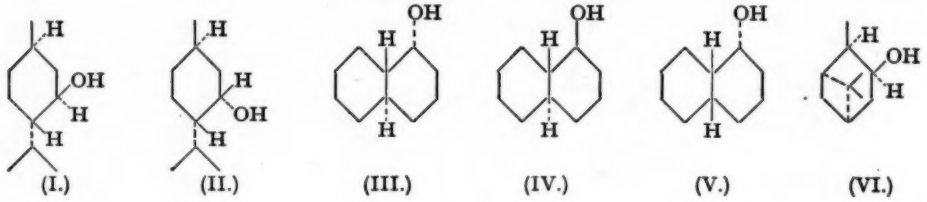
* Formulæ (I), (II), and (VI) are represented in the correct *absolute* stereochemical arrangements (see Fredga and Miettinen, *Acta Chem. Scand.*, 1947, **1**, 371). Dotted bonds project *below* the plane of the paper.

decompositions of which have been described in the literature. Thus (−)-pinocampheol (VI) (Schmidt, *Ber.*, 1944, **77**, 544) methyl xanthate decomposes to give mainly δ-pinene (IX) (Gildemeister and Köhler, *Wallach Festschrift*, 1909, 414; compare Tschugaeff, *J. Russ. Phys. Chem. Soc.*, 1907, **39**, 1330) instead of the alternative α-pinene (X). Also (−)-*neo*thujyl alcohol (VII) (Short and Read, *J.*, 1938, 2016; 1939, 1040) furnishes, as the methyl xanthate, β-thujene (XI) (Tschugaeff and Fomin, *Ber.*, 1912, **45**, 1293) and not α-thujene (XII). Since, however, the latter hydrocarbon is obtained by the pyrolysis of the methyl xanthate of (+)-*iso*thujyl alcohol (*idem*, *J. Russ. Phys. Chem. Soc.*, 1910, **42**, 497), this alcohol must now be assigned the configuration shown in (VIII) (compare Short and Read, *loc. cit.*), whilst *neoiso*-thujyl alcohol must be its hydroxylic epimer.

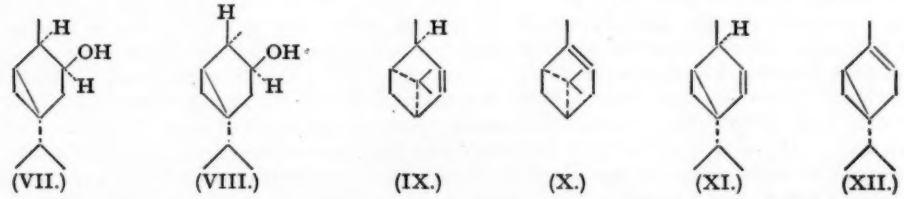
In all the cases so far considered *cis*-elimination has been feasible, in principle, in a direction away from the bridgehead. It is of interest, therefore, to establish the reason for preferential *cis*-elimination towards the bridgehead when this is stereochemically possible. It is now

* It is important to distinguish between the use of the word unimolecular as employed by Hughes, Ingold, and their collaborators for certain heterolytic reactions, occurring in solution, and unimolecular as generally employed in speaking of certain gas reactions. In this paper the word is used exclusively in the latter sense.

universally recognised that the homolytic bond dissociation energies of C–X bonds, where X = H, OH, Cl, Br, I, etc., diminish markedly in the series primary, secondary, tertiary



(I.) (II.) (III.) (IV.) (V.) (VI.)

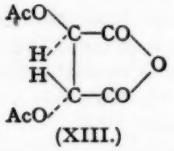


(VII.) (VIII.) (IX.) (X.) (XI.) (XII.)

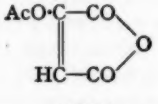
(compare Steacie, " Atomic and Free Radical Reactions," pp. 77 *et seq.*, A.C.S. Monograph No. 102, 1946). It would be expected, therefore, that unimolecular elimination of H–X should also proceed with decreasing activation energy in the series $-\overset{|}{C}-X > >\overset{|}{C}-X > >\overset{|}{C}-X$. It is well illustrated by the series $CH_3{\cdot}CH_2Cl$ (E_A, 60·8 kcals.) > $(CH_3)_2CHCl$ (E_A, 50·5 kcals.) > $(CH_3)_3{\cdot}CCl$ (E_A, 41·4 kcals.), which we have already established (Barton *et al., loc. cit.*). The same conclusion, of course, applies for the elimination of H–X in the series $-\overset{|}{C}-H > >\overset{|}{C}-H > >\overset{|}{C}-H$. Here the X grouping is the same throughout and is attached to the neighbouring carbon atom. The latter is secondary in the alicyclic compounds considered in this paper. Amongst compounds listed in the table it is significant that the methyl xanthate of (+)-*iso*thujyl alcohol decomposes at a much lower temperature (130°) than that of (−)-*neo*-thujyl alcohol (183°). Since the non-exponential terms of unimolecular thermal decompositions of the type under consideration here are normally within a power of 10 of 10^{13} (see Barton and Head, forthcoming paper), these decreases in activation energy are the main factor influencing the reaction velocity and thus explain the preferential elimination towards the bridgehead.

Although the deacylation and dehydration reactions which are discussed below have not been proved, except by the stereochemical requirements of *cis*-elimination, to be unimolecular, it is very probable by analogy that they do have this characteristic. Thus the thermal decompositions of *tert.*-butyl acetate and *tert.*-butyl propionate (Rudy and Fugassi, *J. Phys. Colloid Chem.*, 1948, **52**, 357; Warrick and Fugassi, *ibid.*, p. 1314) are of this type, as are the thermal dehydrations of *tert.*-butyl and *tert.*-amyl alcohols (Schultz and Kistiakowsky, *J. Amer. Chem. Soc.*, 1934, **56**, 395).

Amongst the thermal decomposition reactions of acylates to give olefin and carboxylic acid, the pyrolysis of the diacetate of tartaric anhydride (XIII) should be mentioned. This reaction gives, as final product, C_3O_2 (Ott, *Ber.*, 1914, **47**, 2391; Ott and Schmidt, *ibid.*, 1922, **55**, 2126), but it undoubtedly proceeds *via* acetoxymaleic anhydride (XIV) (Hurd, " The Pyrolysis of Carbon Compounds," 1929, p. 536) and therefore must involve *cis*-elimination.



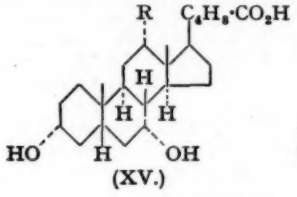
(XIII.)

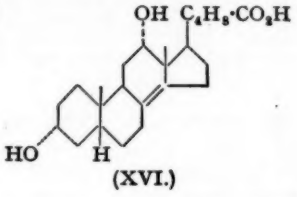


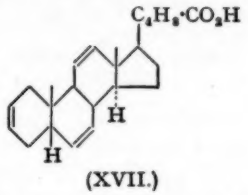
(XIV.)

Some important examples of *cis*-elimination have been discovered in the steroid field. In cholic acid (XV; R = OH) the 7-hydroxyl has been proved, from degradational experiments by Windaus and von Schoor (*Z. physiol. Chem.*, 1925, **148**, 225; compare Iwasaki, *ibid.*, 1936, **244**, 181) on the related chenodeoxycholic acid (XV; R = H), to possess the (α)-orientation, *i.e.*, to lie in the *trans*-relationship to the $C_{(8)}$-hydrogen atom. As is well known, cholic acid is very sensitive to acid dehydrating agents (compare Grand and Reichstein, *Helv. Chim. Acta*, 1945, **28**, 344), *trans*-elimination occurring with initial formation of the corresponding Δ^7-acid.

Depending on the conditions, the latter may be isomerised to the corresponding $\Delta^{8(14)}$-acid, apocholic acid (XVI). As we have pointed out previously (Barton, *J.*, 1946, 1116), unsaturated bile acids with the ethylenic linkage in the 7(8), 8(9), or 8(14) positions cannot be hydrogenated except under drastic conditions. Now, when cholic acid is pyrolysed it affords, as main product, " α "-cholatrienic acid which must be formulated as (XVII), since it is easily hydrogenated (compare below) to the saturated cholanic acid (XVIII) (Wieland and Weil, *Z. physiol. Chem.*,


(XV.)


(XVI.)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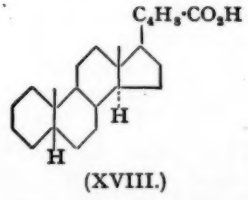
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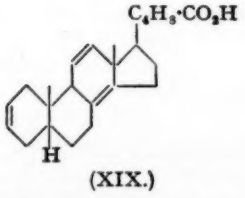
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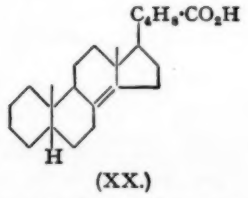
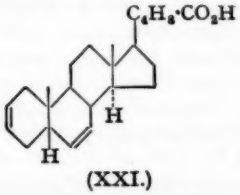
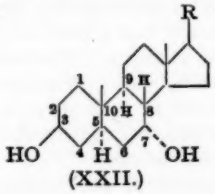
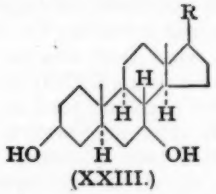

(XX.)

1912, **80**, 287). The formation of the Δ^6-ethylenic linkage is a demonstration of *cis*-elimination The pyrolysis of apocholic acid affords " β "-cholatrienic acid (XIX), which in contrast is hydrogenated to " β "-cholenic acid (XX) (Borsche and Todd, *Z. physiol. Chem.*, 1931, **197**, 173; Wieland and Deulofeu, *ibid.*, 1931, **198**, 127). Similarly, chenodeoxycholic acid (XV; R = H) readily loses water by ionic *trans*-elimination to give olefinic acids which cannot be hydrogenated (Takahashi, *ibid.*, 1938, **255**, 277; Yamasaki and Takahashi, *ibid.*, 1938, **256**, 21) but on pyrolysis it affords by *cis*-elimination chenocholadienic acid (XXI), which is readily hydrogenated to (XVIII) (Wieland and Reverey, *ibid.*, 1924, **140**, 186).


(XXI.)


(XXII.)

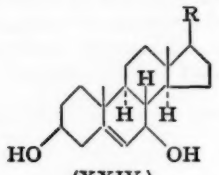

(XXIII.)

The question of the configuration at the 7-position in steroids of the *allo*cholane series has long been a subject for discussion. Wintersteiner and Moore (*J. Amer. Chem. Soc.*, 1943, **65**, 1507) recognised that 7" α "-hydroxycholestanyl acetate was much more resistant to ionic dehydration than the 7" β "-epimer. Recently Fieser, Fieser, and Chakravarti * (*ibid., loc. cit.*) have compared the reactivity of these epimers towards phosphorus oxychloride in pyridine solution. Whereas, the 7" β "-isomer was smoothly dehydrated to cholest-7-en-3(β)-yl acetate (compare Buser, *Helv. Chim. Acta*, 1947, **30**, 1385) the 7" α "-isomer gave the corresponding 7-chloro-compound. This is exactly comparable to the behaviour of (−)-menthol and (+)-*neo*-menthol with phosphorus pentachloride (Zeitschel and Schmidt, *loc. cit.*). The former gives the corresponding chloride but the latter (*trans*-elimination) affords *p*-menth-3-ene. Fieser, Fieser, and Chakravarti concluded, therefore, that the trivial indices at the 7 position should be inverted. This is also in agreement with the (possibly ambiguous) optical rotation evidence discussed by Plattner and Heusser (*Helv. Chim. Acta*, 1944, **27**, 748). Finally, this assignment of configuration is confirmed by pyrolysis evidence. Whereas the 7-benzoate 3-acetate of the 7" β "-epimer (XXII; R = C_8H_{17}) furnished cholest-6-en-3(β)-yl acetate by *cis*-elimination of benzoic acid, the corresponding derivative of the 7" α "-epimer (XXIII) gave cholest-7-en-3(β)-yl acetate (Barton and Rosenfelder, *J.*, in the press).

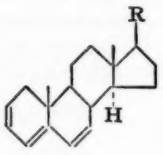
A similar inversion of trivial indices is required for the 7-position in 7-hydroxycholesterol and analogous compounds. Thus the 7" α "-benzoyloxy-derivative of cholesteryl acetate

* We are very much indebted to Professor L. F. Fieser for a copy of this paper before publication.

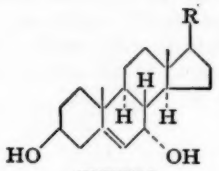
readily gives 7-dehydrocholesteryl acetate on pyrolysis. The parent diol must therefore be 3(β) : 7(β) as in (XXIV; R = C_8H_{17}). On the other hand, the pyrolysis of the epimeric



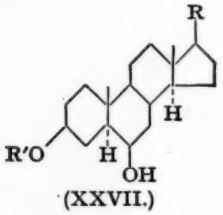
(XXIV.)



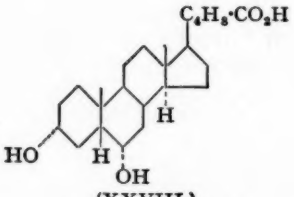
(XXV.)



(XXVI.)



(XXVII.)



(XXVIII.)

7" β "-benzoyloxy-compound (Wintersteiner and Ruigh, *J. Amer. Chem. Soc.*, 1942, **64**, 2453) gives what must now be formulated as cholesta-2 : 4 : 6-triene (XXV; R = C_8H_{17}), and therefore the parent diol must be 3(β) : 7(α) as in (XXVI; R = C_8H_{17}).* This is in agreement with the optical rotation evidence (Bide, Henbest, Jones, and Wilkinson, *J.*, 1948, 1788). A similar situation obtains in the derivatives of 3(α) : 7-dihydroxycholest-5-ene which have been studied by Windaus and Naggatz (*Annalen*, 1939, **542**, 204), although here configurations cannot be assigned on the basis of the optical-rotation evidence. The 3(α) : 7" α "-dibenzoate furnished (XXV; R = C_8H_{17}) on pyrolysis, whereas the 3(α) : 7" β "-dibenzoate split out benzoic acid to give 7-dehydro*epi*cholesteryl benzoate. The trivial indices are, therefore, correctly assigned, and the dibenzoates are 7(α) and 7(β) respectively.

The pyrolysis of the 6-benzoate of 3(β)-acetoxycholestan-6(β)-ol (XXVII; R = C_8H_{17}, R' = Ac) also proceeds, as expected, by *cis*-elimination to give cholest-6-en-3(β)-yl acetate. Another example involving the 6-position is the pyrolysis of hyodeoxycholic acid (XXVIII) which affords what must now be regarded as chola-2 : 6-dienic acid, because it is hydrogenated to give cholanic acid (XVIII) in about 90% yield (Windaus and Bohne, *Annalen*, 1923, **433**, 278). Had the pyrolysis product been chola-4 : 6-dienic acid (Wieland *et al.*, *Z. physiol. Chem.*, 1936, **241**, 47) or an acid with a Δ^5-ethylenic linkage then a major proportion of *allo*cholanic acid would have been expected on hydrogenation.

It will be clear from the examples discussed above that the concept of *cis*-elimination in unimolecular pyrolyses can play as useful a role in elucidating stereochemical relationships as has been played in the past by the idea of *trans*-elimination in many ionic reactions.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

[*Received, April 7th*, 1949.]

* The alternative formulation for the cholestatriene with the ethylenic linkages at the 3 : 5 : 7-positions (compare Windaus and Naggatz, *Annalen*, 1939, **542**, 204) is actually excluded by the absorption-spectrum evidence. The 2 : 4 : 6-triene should absorb at 310 mμ. in ether, the 3 : 5 : 7-triene at 320 mμ. (Fieser, Fieser, and Rajagopalan, *J. Org. Chem.*, 1948, **13**, 800). The triene obtained by pyrolysis had λ max. at 302 mμ. in ether (Eckhardt, *Ber.*, 1938, **71**, 461).

465. *A Novel Synthesis of Histidine.*

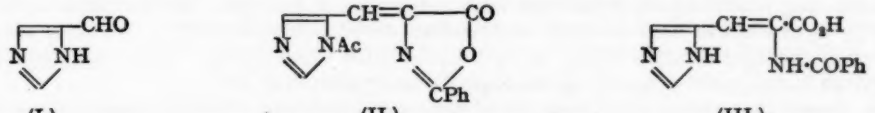
By A. C. Davis and A. L. Levy.

Dithiohydantoin and 2-phenyl-4-ethoxymethyleneoxazolone condense at room temperature in presence of triethylamine and sodium methoxide to give *methyl α-benzamido-β-(2 : 4-dimercapto-5-glyoxalinyl)acrylate* (VII) (93%), the intensely coloured *oxazolone* (VI) being an intermediate. (VII) is simultaneously reduced and desulphurised by Raney nickel at room temperature to give DL-N^{α}-*benzoylhistidine methyl ester* (42%), hydrolysed by acid to DL-histidine. The amino-acid is also made in 53% overall yield by reducing, with red phosphorus and hydriodic acid, the condensation product of 5-formylglyoxaline with 2-mercaptothiazol-5-one (X).

A new synthetic approach to the glyoxaline nucleus was demonstrated (Cook, Heilbron, and Levy, "Studies in the Azole Series," Part II, *J.*, 1947, 1598) by the desulphurisation of 2 : 4-dithio-5-phenylhydantoin with Raney nickel to give 5(4)-phenylglyoxaline. With the exception of the purines, which have already been considered in the papers of the Azole Series, the most important natural compounds containing the glyoxaline nucleus are those related to histidine (see Fox, *Chem. Reviews*, 1943, **32**, 47), and the present communication concerns a synthesis of this amino-acid from dithiohydantoin.

Three previous synthetic routes to histidine are recorded in the literature. Pyman's classical synthesis (*J.*, 1911, **99**, 1386) employed 5(4)-hydroxymethylglyoxaline, built up in five stages from citric acid, the derived chloromethyl compound being condensed with sodiochloromalonic ester; hydrolysis and decarboxylation, followed by amination, produced histidine in 21% yield from hydroxymethylglyoxaline.

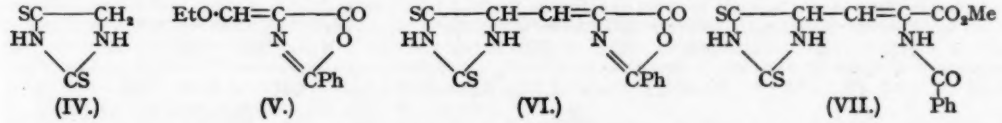
Pyman subsequently (*J.*, 1916, **109**, 186) modified the later stages by oxidation of the 5(4)-hydroxymethylglyoxaline to the corresponding aldehyde (I) (50% yield) and condensed this compound with hippuric acid by an Erlenmeyer synthesis to give the corresponding oxazolone (II) (68—76% yield). Treatment with sodium carbonate caused deacetylation and ring opening of the oxazolone to give the acid (III) (88% yield). (III) was reduced by sodium amalgam to DL-N^{α}-benzoylhistidine (42% yield) which was then hydrolysed to histidine with concentrated hydrochloric acid (overall yield 20% from formylglyoxaline).



(I.) (II.) (III.)

The third and most recent synthesis, due to Albertson (*J. Amer. Chem. Soc.*, 1945, **67**, 308 and 502), was similar in principle to Pyman's earlier method, except that the amino-group was introduced at an early stage as acetamido-malonic or -cyanoacetic ester. The former was condensed with 4(5)-chloromethylglyoxaline (now more readily available in two stages from fructose), and the product simultaneously hydrolysed and decarboxylated to histidine, in 18% yield from cane sugar.

In "Studies in the Azole Series," Part III, Cook, Heilbron, and Levy (*J.*, 1948, 207) recorded the preparation of 2 : 4-dithiohydantoin (IV) in 67% yield from aminoacetonitrile, and demonstrated the presence of an active methylene group in this compound by its ready condensation with acetone to yield 2 : 4-dithio-5-*iso*propylidenehydantoin. For the analogous

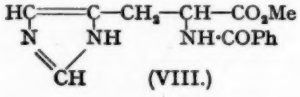


(IV.) (V.) (VI.) (VII.)

introduction of an amino-acid residue, the aldehyde $OHC{\cdot}CH(NH_2){\cdot}CO_2H$ would be required, and, as a result of chemical studies on penicillin, this was readily available in the form of its derivative, 2-phenyl-4-ethoxymethyleneoxazolone (V).

When (IV) and (V) were brought together in cold methanol containing one equivalent of triethylamine, an intense colour at once developed, due to the cyanine-like condensation product, 2-*phenyl*-4-(2′ : 4′-*dimercapto*-5′-*glyoxalinylmethylene*)*oxazolone* (VI) which separated, when the mixture was kept, as a *monotriethylamine* salt in fine purple-red needles. The parent thiol was readily obtained as a purple-black microcrystalline powder on acidification of an

aqueous solution. When either of these compounds was treated with Raney nickel at room temperature, desulphurisation occurred, as shown by rapid loss of colour, but the product was firmly bound to the nickel and could not be removed by extraction with solvents, including pyridine or aqueous sodium hydroxide. This difficulty was overcome when it was observed that another condensation of (IV) and (V) under more vigorous conditions yielded, instead of (VI), a yellow compound isolated as its *triethylamine* salt. This analysed for (VI) with the addition of the elements of methanol, and was evidently the methyl ester (VII). (VII) also was rapidly desulphurised by Raney nickel in ethanol, but in this case a colourless crystalline product was recovered, in 42% yield, of m. p. 151°. This was saturated, free from sulphur, gave a strong Pauly reaction for the glyoxaline nucleus, and was identified as DL-N^{α}-*benzoylhistidine methyl ester* (VIII), and it was therefore apparent that reduction of the double bond in (VII) had accompanied desulphurisation.



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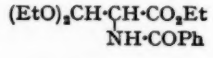


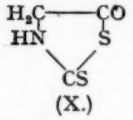
(IX.)

(VII) could also be obtained from (VI) by warming with methanol containing triethylamine, but it was most conveniently prepared in 93% yield directly from (IV) and (V) by treatment with triethylamine followed by sodium methoxide. Further evidence that condensation with dithiohydantoin had preceded opening of the oxazolone ring in such circumstances was given by the failure of ethyl norpenaldate diethyl acetal (IX) to condense under comparable conditions. Treatment of (VI) with methyl sulphate and alkali gave a *tetramethyl* derivative; under the same conditions (VII) also afforded this compound, whilst dithiohydantoin itself gave a dimethyl derivative, formulated as 2 : 4-*dithio*-1 : 3-*dimethylhydantoin* since alkaline hydrolysis did not yield methanethiol.

While this material was available, it was thought of interest to treat DL-N^{α}-benzoylhistidine, obtained readily by hydrolysis of the ester with alkali, with aniline in the presence of cysteine-activated papain (Bergmann and Fraenkel-Conrat, *J. Biol. Chem.*, 1937, **119**, 707), but no asymmetric synthesis of the anilide took place, possibly owing to the basic nature of the glyoxaline ring hindering its separation from a solution of low pH. Further hydrolysis with hot 20% hydrochloric acid yielded DL-histidine dihydrochloride (70%; Pyman, *loc. cit.*), prepared in this case directly (83%) by hydrolysis of the ester (VIII). Thus, the overall yield of histidine in this three-stage synthesis from dithiohydantoin is 32%.

It is known that serine, in certain peptide-like combinations, is readily transformed into an ethoxymethyleneoxazolone (Copp, Duffin, Smith, and Wilkinson, "The Chemistry of Penicillin," Princeton Univ. Press, p. 747), so that in the above synthesis histidine is in effect constructed from glycine, ammonia, carbon disulphide, and serine. This result suggests that the amino-acid may arise *in vivo* by the elaboration of glycine, carbon dioxide, and ammonia into hydantoin, followed by condensation with serine and reduction to a glyoxaline. 1-Methylhistidine would be derived in this way from sarcosine.

It was shown ("Studies in the Azole Series," Part III, *loc. cit.*) that 5-amino-2-mercaptothiazole yielded dithiohydantoin with bases and 2-mercaptothiazol-5-one (X) with acids, and it seemed therefore an attractive possibility to condense these two substances through ethyl orthoformate, and, proceeding as above, to effect a synthesis of histidine almost entirely from aminoacetonitrile and carbon disulphide. Indeed, 2-mercapto-4-ethoxymethylenethiazol-5-one



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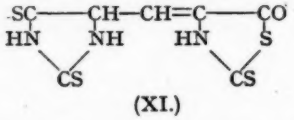
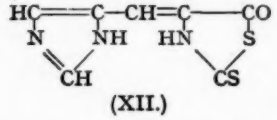


(XI.)



(XII.)

condensed readily with dithiohydantoin in methanol in presence of triethylamine as catalyst, to give the almost black compound (XI). With Raney nickel this was soon decolorised, but as in the case of (VI) the product could not be eluted from the nickel. It was noted that (XI) was remarkably stable, being recovered apparently unchanged after vigorous treatment with caustic alkali and with sodium amalgam.

It was possible, however, to effect a synthesis of histidine from 2-mercaptothiazol-5-one (X) by the method described in the Azole series, Parts VII and XIX (Chatterjee, Cook, Heilbron, and Levy, *J.*, 1948, 1337; Billimoria and Cook, in the press). 4(5)-Formylglyoxaline (I)

was condensed with 2-mercaptothiazol-5-one in glacial acetic acid to yield 80% of *2-mercapto-4-[4′(5′)-glyoxalinylmethylene]thiazol-5-one* (XII). When this compound was heated under reflux with red phosphorus and hydrogen iodide in acetic acid, DL-histidine was obtained in 64% yield (as the dipicrate). This represents double the yield and half the number of stages of the comparable Erlenmeyer synthesis (Pyman, *loc. cit.*).

Experimental.

Condensation of Dithiohydantoin and 2-Phenyl-4-ethoxymethyleneoxazolone.—Dithiohydantoin (4·3 g.) and 2-phenyl-4-ethoxymethyleneoxazolone (6·6 g.; Barber and Slack, *op. cit.*, p. 803) were shaken with water (25 c.c.) and triethylamine (7 g.) until dissolved (*ca.* 10 minutes) and the deep purple-red solution was set aside at room temperature for 1 hour. On acidification, *2-phenyl-4-(2′:4′-dimercapto-5′-glyoxalinylmethylene)oxazolone* (VI) (8·7 g.; 90%) was obtained as a reddish-purple, infusible powder (Found: N, 13·7. $C_{12}H_8O_2N_2S_2$ requires N, 13·9%).

Dithiohydantoin (5 g.) and 2-phenyl-4-ethoxymethyleneoxazolone (8·25 g.) were powdered finely and suspended in methanol (40 c.c.). On the addition of triethylamine (6 g.) all the solid dissolved and the temperature rose to 40°. After 36 hours the product (8·8 g.; 57%) was filtered off, washed with acetone and ether, and recrystallised from methanol to give the *mono-triethylamine* salt of (VI) as dark purple-red needles, m. p. 297—300° after darkening at 180° and sintering at 265° (Found: C, 56·3; H, 6·0; N, 14·2. $C_{19}H_{24}O_3N_4S_2$ requires C, 56·4; H, 6·0; N, 13·9%). Evaporation of the filtrate yielded an oily residue, which dissolved in water and was acidified, to yield 4·2 g. (36%) of the free thiol (VI).

Methyl α-Benzamido-β-(2:4-dimercapto-5-glyoxalinyl)acrylate (VII).—(*a*) Dithiohydantoin (2 g.) and 2-phenyl-4-ethoxymethyleneoxazolone (3·3 g.) were heated under reflux for 5 minutes in methanol (20 c.c.) containing water (1 c.c.) and triethylamine (3 c.c.). After the mixture had been cooled and kept overnight at room temperature, the crystalline mass was broken up, filtered off, and washed with methanol, leaving yellow needles (3·3 g.; 53%), m. p. 180° (decomp.). The *triethylamine* salt of methyl α-benzamido-β-(2:4-dimercapto-5-glyoxalinyl)acrylate was recrystallised from water (Found: C, 55·1; H, 6·45. $C_{20}H_{28}O_3N_4S_2$ requires C, 55·0; H, 6·5%).

(*b*) Dithiohydantoin (10·5 g.) and 2-phenyl-4-ethoxymethyleneoxazolone (17·3 g.) were treated with methanol (40 c.c.) and triethylamine (11 c.c.), whereupon the temperature rose almost to boiling point. After 0·5 hour at room temperature, 2N-methanolic sodium methoxide (80 c.c.) was added with ice-cooling, and the solution kept for 12 hours at 0°. Dilution with water (1 l.) and acidification with 2N-hydrochloric acid then gave the methyl ester (VII) (25 g.; 93·5%) as a fine yellow powder, m. p. 185—190°, undepressed by admixture with the compound obtained by acidification of an aqueous solution of the above triethylamine salt.

Methylation Experiments.—The oxazolone (VI) (2 g.) was dissolved in 10% aqueous sodium hydroxide (50 c.c.); a colour change from purple to orange-yellow, occurring in 2—3 minutes, indicated opening of the oxazolone ring. Methyl sulphate (6 c.c.) was added gradually with shaking and ice-cooling. The crude *tetramethyl* derivative of (VI) which separated (2·3 g.; 96%) recrystallised from ethanol in thick colourless prisms, m. p. 176° (Found: C, 54·2; H, 5·2; N, 11·5. $C_{17}H_{19}O_3N_3S_2$ requires C, 54·1; H, 5·1; N, 11·1%). During the recrystallisation a *compound* was separated, which formed small felted yellow needles, m. p. 258—260°, crystallising from a large volume of ethanol (Found: C, 54·0; H, 4·15; N, 13·4. $C_{18}H_{16}O_3N_4S_2$ requires C, 54·0; H, 4·0; N, 14·0. $C_{28}H_{32}O_3N_6S_4$ requires C, 54·0; H, 4·2; N, 13·5%). The same tetramethyl compound was obtained from the methyl ester (VII) or the derived triethylamine salt, by methylation under the above conditions. The tetramethyl derivative added on bromine in chloroform, yielding colourless needles, m. p. 169—171° (decomp.), but was resistant to desulphurisation with Raney nickel.

Methylation of dithiohydantoin with an excess of methyl sulphate and alkali gave only a dimethyl derivative, m. p. 90°, which crystallised in fine colourless needles from light petroleum (b. p. 80—100°) (Found: C, 37·85; H, 5·2; N, 17·3. $C_5H_8N_2S_2$ requires C, 37·5; H, 5·0; N, 17·5%). In view of its failure to yield methanethiol when boiled with 2N-caustic alkali, the structure *1:3-dimethyl-2:4-dithiohydantoin* was assigned to this substance.

DL-N^a-*Benzoylhistidine Methyl Ester.*—Methyl α-benzamido-β-(2:4-dimercapto-5-glyoxalinylmethylene)acrylate (VII) (4 g.) in boiling ethanol (10 c.c.) was treated with Raney nickel (prepared according to *Org. Synth.*, **21**, 15) (16·2 g.), the solution becoming colourless. After being heated under reflux for a further five minutes, the mixture was filtered through a Soxhlet thimble, and the nickel residue continously extracted with ethanol for 2 hours, in order to recover the maximum possible amount of product. The combined solutions were evaporated *in vacuo* to a syrup, dissolved in acetone (5 c.c.), filtered from insoluble material, and re-evaporated. After 1 day, crystallisation was complete, giving 1·4 g. (43%) of DL-N^a-*benzoylhistidine methyl ester*, which crystallised in sheaves of colourless needles, m. p. 150—151°, from acetone on the addition of light petroleum (Found: C, 61·4; H, 5·6; N, 15·7. $C_{14}H_{15}O_3N_3$ requires C, 61·5; H, 5·5; N, 15·4%).

The ester was hydrolysed by 10% aqueous sodium hydroxide at 100° to DL-N^a-benzoylhistidine, m. p. 248°, which was treated, under the conditions employed by Dekker and Fruton (*J. Biol. Chem.*, 1948, **173**, 471) for benzoylmethionine, with papain and aniline at pH 5. No separation of anilide occurred during 1 week at 40°, or when the experiment was repeated at pH 6 or 7. Seeding with DL-N^a-benzoylhistidine anilide, m. p. 250°, prepared by heating DL-N^a-benzoylhistidine at 100° with acetic anhydride and treating the resulting golden-yellow 2-phenyl-4-(1′-acetyl-5′-glyoxalinyl)oxazolone, m. p. 183—184°, with aniline in chloroform, was also without avail.

DL-*Histidine.*—DL-N^a-Benzoylhistidine methyl ester (0·515 g.) and concentrated hydrochloric acid (30 c.c.) were set aside overnight and then heated for 1·5 hours under reflux. Benzoic acid separated and was removed by ether-extraction. Evaporation *in vacuo* left a syrup, crystallising, on cooling, in sheaves of colourless needles, m. p. 200° (indefinite) (0·478 g., theoretical quantity). From the m. p.

it appears that these were substantially the dihydrochloride (m. p. 235° according to Pyman, *loc. cit.*). The hydrochloride was converted directly into the dipicrate dihydrate (1·03 g., 83%) which formed light orange-yellow needles, m. p. 90—100°; these were recrystallised from water (charcoal), yielding pale yellow needles, m. p. 103° after sintering at 99—100°, not depressed by admixture with an authentic specimen.

Condensation of Dithiohydantoin and 2-Mercapto-4-ethoxymethylenethiazol-5-one.—2-Mercapto-4-ethoxymethylenethiazol-5-one (1·7 g.) (Cook, Heilbron, and Levy, *loc. cit.*) was dissolved in boiling methanol (10 c.c.) containing triethylamine (2 g.; 2 equivs.); dithiohydantoin (1·3 g.) (*idem, loc. cit.*) was added, and, after all the material had dissolved, the solution was cooled and kept for 2 hours at room temperature. By dilution with water (40 c.c.) and acidification with mineral acid, an oil was obtained which was solidified under methanol (20 c.c.). 2-Mercapto-4-(2′ : 4′-dimercapto-5-glyoxalinylmethylene)thiazol-5-one (1·5 g.; 79%) formed a purple-black infusible powder.

Similar intensely-coloured compounds were obtained by condensation of the following components, but were not analysed: 2-ethylthio-4-ethoxymethylenethiazolone and 2-thiohydantoin (red, m. p. above 290°), and 2 : 4-dithiohydantoin (purple-black, m. p. indefinite); 2-mercapto-4-ethoxymethylenethiazolone and 2-thio-3-methylthiazolid-2 : 4-dione [olive-green needles, m. p. 195° (decomp.)]. All these compounds had a green lustrous reflex in the solid state, showing their true colour when finely-ground or when viewed through the microscope. Similar compounds were obtained also from 2-phenyl-4-ethoxymethyleneoxazolone and 2-thiohydantoin [orange-yellow needles, m. p. 153° (decomp.)], and 2-thio-3-methylthiazolid-2 : 4-dione [yellow felted needles, m. p. 260° (decomp.)].

DL-*Histidine from 4(5)-Formylglyoxaline.*—(This synthesis was performed by Mr. G. F. Woods, to whom we express our thanks for permission to include it in the present paper.) 2-Mercaptothiazol-5-one (2·3 g.) and 4(5)-formylglyoxaline (2·6 g.) [prepared by the oxidation (Pyman, *loc. cit.*) of 4(5)-hydroxymethylglyoxaline (*Org. Synth.*, **24**, 64)] were together dissolved in glacial acetic acid (25 c.c.). The solution was heated to boiling, whereupon an exothermic reaction commenced and boiling maintained itself for several minutes. On cooling, *2-mercapto-4-(5′-glyoxalinylmethylene)thiazol-5-one* (3·8 g.; 80%), m. p. 258—260°, separated and recrystallised from acetic acid as yellow-green plates, m. p. 260° (decomp.) (Found: C, 39·9; H, 2·2; N, 19·65. $C_7H_5ON_3S_2$ requires C, 39·8; H, 2·4; N, 19·85%).

The above thiazolone (1·5 g.) with red phosphorus (1·5 g.) and hydriodic acid (50% aq., 2·5 c.c.) in acetic acid (25 c.c.), and acetic anhydride (5 c.c.) was boiled under reflux for 1·5 hours. By this time all the soluble material had dissolved and the excess of phosphorus was removed by filtration through glass wool. The solution was then evaporated to leave a syrupy residue, extraction of which with ether left a semi-crystalline residue. This crude hydriodide was dissolved in water and converted into the dipicrate, m. p. 187—188° (after drying at 100°) (2·8 g., 64%), from which the free amino-acid was prepared by the method of Pyman (*loc. cit.*). Thus obtained, the amino-acid formed colourless quadrilateral plates, m. p. 281—283°, which rose to 283—284° after several recrystallisations from water and was not depressed by admixture with an authentic specimen (Found: N, 27·0. Calc. for $C_6H_9O_2N_3$: N, 27·1%).

We are deeply indebted to Sir Ian Heilbron, D.S.O., F.R.S., and Dr. A. H. Cook for their helpful interest in this work, to the Department of Scientific and Industrial Research for a Senior Research Award (A. L. L.), and to the Rockefeller Foundation for a grant (A. C. D.).

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466. *Syntheses of Fluoranthenes. Part I.* Michael Addition of Fluorene and of Methyl Fluorene-9-carboxylate to Crotononitrile. Syntheses of 2-Methyl- and of 2 : 4-Dimethyl-fluoranthene.*

By S. HORWOOD TUCKER.

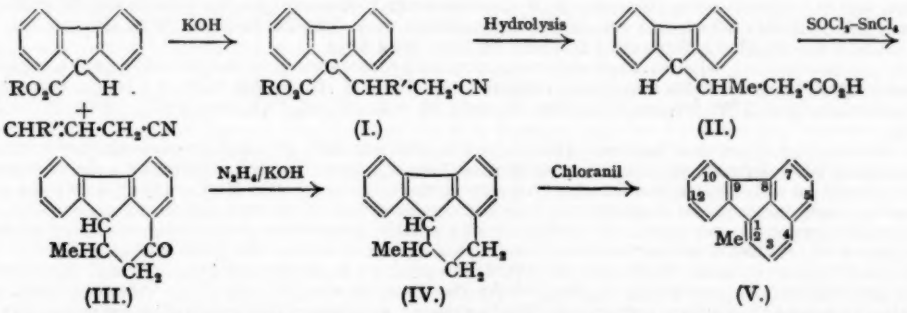
Methyl fluorene-9-carboxylate has been used in a Michael reaction with allyl cyanide (or crotononitrile which reacts as allyl cyanide) to prepare 2-(9′-carbomethoxy-9′-fluorenyl)propyl cyanide (I; R = R′ = Me). Hydrolysis of this cyanide has given rise to expected intermediates of the final product *β-9-fluorenylbutyric acid* (II), which has been cyclised to 4-keto-2-methyl-1 : 2 : 3 : 4-tetrahydrofluoranthene (III). This compound has given rise to (*a*) by reduction, followed by dehydrogenation, 2-methylfluoranthene, and (*b*) by a Grignard reaction, followed by dehydrogenation, to 2 : 4-dimethylfluoranthene.

The hydrogenation products of 2 : 4-dimethylfluoranthene have been investigated.

IN the Michael reaction of fluorene with vinyl cyanide, in the presence of a base, two molecules of the cyanide add to one of fluorene to give 9 : 9-di-(2′-cyanoethyl)fluorene: monocyanoethylation has not been accomplished. On the other hand the less reactive crotononitrile reacts in unimolecular proportions with fluorene to give 2-9′-fluorenylpropyl cyanide (Bruson, *J. Amer. Chem. Soc.*, 1942, **64**, 2457). Bruson's reaction is limited, as far as fluorene is concerned, to these two reactions. Accordingly, in order to render the Michael reaction of wider application,

* This work is a continuation of "The Condensation of Fluorene with Acetone," Part VI, this vol., p. 632.

methyl (or ethyl) fluorene-9-carboxylate has been used. This procedure has two advantages: (*a*) the available 9-hydrogen atom is rendered more reactive, and (*b*) only one hydrogen atom is utilisable. This ester has been found to be of use, not only in condensations with αβ-unsaturated cyanides, but also with αβ-unsaturated ketones (the latter syntheses, as also corresponding ones with methyl indene-1-carboxylate will be reported later). Thus the synthesis of 2-methylfluoranthene has been accomplished by the series of reactions shown below; the intermediate (I) need not be isolated.



β-9-*Fluorenylbutyric acid* (II) was prepared in one operation by treating allyl cyanide with methyl fluorene-9-carboxylate in the presence of potassium hydroxide in 2-methoxyethanol. The intermediate 2-(9′-*carbomethoxy*-9′-*fluorenyl*)*propyl cyanide* (I; R = R′ = Me) was hydrolysed, without isolation, to the acid (II) (79% yield); actually, all the expected intermediates in the above process have been isolated, *viz.*, the ester-cyanide (I; R = R′ = Me), the acid-cyanide (I; R = H, R′ = Me), the cyanide (II, CN for CO_2H), and the corresponding amide. Hydrolysis of the cyanide-ester (I; R = R′ = Me) by a mixture of water, and sulphuric and acetic acid (Reichstein, *Helv. Chim. Acta*, 1937, **20**, 1418) gave β-(9-*carboxy*-9-*fluorenyl*)-*butyric acid* (I; R = H, R′ = Me, CO_2H for CN).

β-9-Fluorenylbutyric acid (II), by the usual method of treatment with thionyl chloride or phosphorus pentachloride in benzene, and then with stannic chloride, gave 2-*methyl*-4-*keto*-1 : 2 : 3 : 4-*tetrahydrofluoranthene* (III), which by the Huang-Minlon modification (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) of the Wolff–Kishner method of reduction gave 2-*methyl*-1 : 2 : 3 : 4-*tetrahydrofluoranthene* (IV). (IV) was dehydrogenated by a boiling solution of chloranil in xylene to 2-methylfluoranthene (V), m. p. 72—75°.*

Consideration of the formula (III) led obviously to a new synthesis of 2 : 4-dimethylfluoranthene (Forrest and Tucker, *J.*, 1948, 1137): methylmagnesium iodide and (III) gave, without isolation of the carbinol, 2 : 4-*dimethyl*-1 : 2(?)-*dihydrofluoranthene*, which by means of chloranil in boiling xylene gave 2 : 4-dimethylfluoranthene.

Catalytic hydrogenation of the above dihydro-compound gave 2 : 4-*dimethyl*-1 : 2 : 3 : 4-*tetrahydrofluoranthene*, m. p. 79—81°, different in many properties from the isomer, m. p. 115—117°, previously described (Tucker and Whalley, *J.*, 1949, 634); they are presumably stereoisomers.

The crotononitrile used was prepared (Bruson and Riener, *J. Amer. Chem. Soc.*, 1943, **65**, 22) from allyl cyanide (*Org. Syn.*, **8**, 4; Vogel, *J.*, 1948, 661), but it was eventually found that they gave identical results under the alkaline conditions employed (cf. Buckley, Elliott, Hunt, and Lowe, *J.*, 1947, 1505).

Experimental.

Methyl Fluorene-9-carboxylate.—Fluorene-9-carboxylic acid (52·5 g.), suspended in anhydrous methanol (125 ml.) (Baker and Holdsworth, *J.*, 1947, 724), was treated with dry hydrogen chloride until a clear solution was obtained (15—20 minutes), set aside overnight, and then placed in ice. The pale brown crystals deposited were washed with and crystallised from methanol, giving methyl fluorene-9-carboxylate, m. p. 63—66° (lit., 63°) (47 g.). The residual liquor on treatment with water gave an oil which after being shaken with three changes of cold methanol gave a solid which crystallised from methanol (4·6 g.). The total yield was 51·6 g. (92%).

In one experiment the residual methanolic solution on treatment with water gave a material which crystallised slowly from light petroleum (b. p. 40—60°) after being scratched. Recrystallisation from aqueous methanol gave greenish prisms, m. p. 37—39° (Found: C, 80·0; H, 5·5%).

Ethyl fluorene 9-carboxylate was prepared similarly to the methyl ester. It crystallised readily from methanol or ethanol (scratch) (yield, 83%, m. p. 42—45°) (cf. Delacre, *Bull. Soc. chim.*, 1902, **27**, 881; Wislicenus and Mocker, *Ber.*, 1913, **46**, 2775).

* (V) has been prepared independently and by a different method by Dr. H. Wang, Ph.D. thesis, Edinburgh, 1948; Campbell and Wang, this vol., p. 1513.

β-9-Fluorenylbutyric acid (II) was prepared from methyl fluorene-9-carboxylate and allyl cyanide by two routes, (*A*) with isolation of intermediates, and (*B*) a more direct approach.

(A) *Stepwise Synthesis of β-9-Fluorenylbutyric Acid.*—*2-(9′-Carbomethoxy-9′-fluorenyl)propyl cyanide* (I; R = R′ = Me). Dioxan (5 ml.), potassium hydroxide (0·11 g., 0·2 mol.; powdered and added at once to avoid absorption of water), allyl cyanide (1·01 g., 1·5 mols.), and methyl fluorene-9-carboxylate (2·24 g.; 1 mol.) were mixed in that order, and the clear solution was set aside at room temperature for 4 days. It was then diluted with water and excess of 5% potassium hydroxide solution, and extracted with ether twice, the ether extracts being washed with water and evaporated without drying; finally the oily residue was warmed while a blast of air was passed over it to remove excess of allyl cyanide and solvent, and then dissolved in ethanol. *2-(9′-Carbomethoxy-9′-fluorenyl)propyl cyanide* slowly crystallised (scratch) in octahedra, which felt very soft when crushed, m. p. 72—75° (2·15 g., 73%) (Found: C, 78·4; H, 5·8; N, 4·9. $C_{19}H_{17}O_2N$ requires C, 78·3; H, 5·9; N, 4·8%).

The alkaline extract, when treated with concentrated hydrochloric acid and set aside, gave a crystalline deposit of *2-(9′-carboxy-9′-fluorenyl)propyl cyanide* (I; R = H, R′ = Me) (0·27 g., 10%), softening at 165° and melting at 179° (Found: C, 77·8; H, 5·5; N, 5·3. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·45; N, 5·05%).

In the above preparation, warming the original mixture to 50°, or using an equivalent of potassium hydroxide, of benzyltrimethylammonium hydroxide (38% aqueous solution), sodium hydride, or sodamide caused formation of uncrystallisable oils. Aqueous potassium hydroxide (50%) which, as will be shown in a later communication, is most effective in the condensation of methyl fluorene-9-carboxylate with vinyl cyanide, gave a lower yield. Even the use of a smaller proportion (1·05 mols.) of allyl cyanide had a similar effect. When 2-methoxyethanol was used in place of dioxan the yield was as good, but when larger quantities were used frequently no crystalline product could be isolated, although hydrolysis of the oil obtained always gave a high yield of β-9-fluorenylbutyric acid (II) [see (B)]. Keeping the (dioxan) mixtures for longer than 4 days had no definite advantage: shortening the period of reaction to 1 day gave lower but considerable yields.

2-(9′-Carbethoxy-9′-fluorenyl)propyl cyanide was similarly prepared from ethyl fluorene-9-carboxylate (2·38 g.). It crystallised from methanol in large prisms, m. p. 74—76° (2·12 g., 70%) (Found: C, 78·8; H, 6·3; N, 4·9. $C_{20}H_{19}O_2N$ requires C, 78·7; H, 6·3; N, 4·6%). Like the corresponding methyl ester these crystals felt soft when powdered. The corresponding acid-cyanide (0·14 g., 5%) was also obtained.

2-9′-Fluorenylpropyl cyanide (II; CN for CO_2H). The ester-cyanide (I; R = R′ = Me) was readily hydrolysed to the corresponding acid-cyanide (I; R = H, R′ = Me) by dissolving it in warm ethanol, adding 10N-potassium hydroxide, and setting the mixture aside (*ca.* 5 minutes) until a drop gave no precipitate with water. Acidification with concentrated hydrochloric acid gave the acid-cyanide, 2-(9′-carboxy-9′-fluorenyl)propyl cyanide (I; R = H, R′ = Me) (*ca.* 100%). When this acid-cyanide or the ester-cyanide was heated with 10N-potassium hydroxide it rapidly effervesced and in a few minutes gave 2-9′-fluorenylpropyl cyanide (II; CN for CO_2H), m. p. 92—93° (high yield). Attempts to effect this decarboxylation by heating the acid at 200° gave unintelligible results. (II; CN for CO_2H) was also readily prepared by interaction of fluorene and crotononitrile in presence of benzyltrimethylammonium hydroxide in dioxan, but in lower yield than that claimed (Bruson, *loc. cit.*).

Attempts to bring about the above hydrolyses of the ester- (or acid-)cyanide to 2-9′-fluorenylpropyl cyanide by 10% potassium hydroxide solution gave only the acid-cyanide: 20% potassium hydroxide solution, with boiling for 3 hours, gave a mixture of products including *β-9-fluorenylbutyric acid* (II) crystallising from benzene–petroleum (60—80°) (1 : 1) and then from methyl cyanide in large rectangular prisms, m. p. 143—147° (Found: C, 80·9; H, 6·3. $C_{17}H_{16}O_2$ requires C, 80·95; H, 6·35%). Heating the ester-cyanide (I; R = R′ = Me) with 50% aqueous potassium hydroxide in ethanol for 1 hour gave the above acid (II) and (insoluble in aqueous alkali) *β-9-fluorenylbutyramide* which crystallised from benzene in nacreous leaflets, m. p. 158—160° after softening at 150° (Found: C, 81·1; H, 6·7; N, 5·9. $C_{17}H_{17}ON$ requires C, 81·3; H, 6·8; N, 5·6%).

β-9-Fluorenylbutyric acid was readily obtained by hydrolysis of either the ester-cyanide (2·91 g.), acid-cyanide (2·77 g.), or 2-9′-fluorenylpropyl cyanide (2·37 g.) by boiling its solution in 2-methoxyethanol (10 ml.) with 10N-potassium hydroxide (15 ml.) for 2—3 hours. Pouring the mixture into water gave a turbid yellow solution (even after 5 hours' boiling). Filtration through charcoal and addition of excess of concentrated hydrochloric acid gave β-9-fluorenylbutyric acid (II) (2·17 g., 86% from the ester-cyanide).

β-(9-Carboxy-9-fluorenyl)butyric acid (I; R = H, R′ = Me, CO_2H for CN). 2-(9′-Carbomethoxy-9′-fluorenyl)propyl cyanide (I; R = R′ = Me) (0·29 g.), glacial acetic acid (5 ml.), concentrated sulphuric acid (2 ml.), and water (2 ml.) were boiled for 3 hours, and the solution was diluted with excess of alkali, filtered from insoluble material (0·02 g.; recrystallised from methanol, m. p. 245°; 9 : 9′-difluorenyl), and treated with concentrated hydrochloric acid, to give, after recrystallisation from methyl cyanide, *β-(9-carboxy-9-fluorenyl)butyric acid* (I; R = H, R′ = Me, CO_2H for CN) as prisms, m. p. 121—123° (turbid melt until 160°) (0·18 g., 64%) (Found: C, 73·2; H, 5·6. $C_{18}O_{16}O_4$ requires C, 73·0; H, 5·4%). When, however, this acid was boiled in, and then crystallised from, toluene it gave nodules softening at 155°, melting slowly to 170° (samples had m. p. 166—170°) (Found: C, 73·7; H, 5·3. The anhydride, $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·1%). Wislicenus and Mocker (*loc. cit.*, p. 2790) obtained an anhydride from (I; R = R′ = H CO_2H for CN).

β-9-Fluorenylbutyric Acid (II) was similarly obtained from 2-9′-fluorenylpropyl cyanide (II; CN for CO_2H) (2·33 g.) by boiling it with glacial acetic acid (25 ml.), concentrated sulphuric acid (5 ml.), and water (5 ml.) for 4—5 hours. Dilution with water and setting the mixture aside gave the acid (II) (2·06 g., 82%), m. p. 143—147°. It was also obtained by heating *β-(9-carboxy-9-fluorenyl)butyric acid* over a free flame until effervescence ceased (good yield).

(B) *Direct Synthesis of β-9-Fluorenylbutyric Acid* (II).—The preparation of (II), without isolation of any intermediate, from methyl fluorene-9-carboxylate and allyl cyanide was effected in 2-methoxyethanol rather than in dioxan. 2-Methoxyethanol (redistilled, b. p. 124°; 12·5 ml.) and potassium hydroxide pellets (0·28 g., 0·2 mol.) were heated to dissolve the latter, the solution was cooled, allyl

cyanide (2·51 g., 1·5 mols.) and then methyl fluorene-9-carboxylate (5·60 g., 1 mol.) were added and set aside with occasional shaking for 7 days. 2-Methoxyethanol (25 ml.) and 10N-potassium hydroxide (35 ml.) were then added and the mixture was boiled. The precipitated oil rapidly dissolved to give a clear green liquid (owing, probably, to hydrolysis of ester-cyanide to acid-cyanide), then after 1 minute suddenly became turbid [decarboxylation to the cyanide (II)], again rapidly clarified (amide formation), and slowly darkened. After boiling for 3 hours the solution was poured into water to give a turbid, yellow, fluorescent liquid, which after filtration through charcoal was treated with concentrated hydrochloric acid until only slightly alkaline, and then rendered acid with glacial acetic acid. The precipitated soft, grey mass was crystallised from methyl cyanide in rectangular plates (5·0 g., 79%) of β-9-fluorenylbutyric acid (II), m. p. 143—147°. A similar experiment in which the mixture was set aside for 4 days and the period of boiling was 4 hours gave almost the same yield (75%) of (II), but the product was yellow. When the mixture was kept for 5 or 24 *hours*, the yields of (II) were 24 and 33%, respectively.

Cyclisation of β-9-Fluorenylbutyric Acid (II) *to 4-Keto-2-methyl-1 : 2 : 3 : 4-tetrahydrofluoranthene* (III).—(II) (5·04 g., 0·02 g.-mol.) was boiled for 10 minutes with excess of thionyl chloride (distilled from linseed oil), the excess of thionyl chloride removed in a vacuum, and dry thiophen-free benzene (10 ml.) added and then a solution of stannic chloride (4·6—4·7 ml., 0·04 g.-mol.) in benzene (5 ml.). After 1 hour a dark brown crystalline solid had separated. The whole mixture was treated with concentrated hydrochloric acid and extracted with hot benzene (the product is nearly insoluble in ether). Since shaking a portion of the benzene extract with 5% potassium hydroxide solution, followed by acidification of the alkaline extract, gave no precipitate of the acid (II), this treatment was dispensed with for the main benzene extract, evaporation of which, followed by crystallisation from ethanol and then from ethyl acetate gave *4-Keto-2-methyl-1 : 2 : 3 : 4-tetrahydrofluoranthene* (III) as cream-coloured leaflets, m. p. 159—160° (2·9 g., 62%) (Found: C, 87·0; H, 6·0. $C_{17}H_{14}O$ requires C, 87·2; H, 6·0%). The use of phosphorus pentachloride [1 or 2 mols. per mol. of (II)] gave lower yields (42%) and some (II) was recovered. The acid (II) was recovered unchanged after being warmed with concentrated sulphuric acid in glacial acetic acid. The *2 : 4-dinitrophenylhydrazone* of (III), prepared in methanol acidified with concentrated sulphuric acid, crystallised in very small scarlet needles from anisole; it darkened at 250° but melted sharply at 276° (decomp.) (Found: C, 66·8; H, 4·45; N, 13·2. $C_{23}H_{18}O_4N_4$ requires C, 66·7; H, 4·35; N, 13·5%).

2-Methyl-1 : 2 : 3 : 4-tetrahydrofluoranthene (IV).—4-Keto-2-methyl-1 : 2 : 3 : 4-tetrahydrofluoranthene (III) (1·17 g.), potassium hydroxide (0·3 g.), hydrazine (90%; 1·0 ml.) in 2 : 2′-dihydroxydiethyl ether (4 ml.) were boiled for 1 hour, the water was removed by distillation, the surrounding bath being maintained at 195—200° for 3 hours. An air blast was used to remove water during the first 15 minutes. The cooled mixture was treated with hydrochloric acid. The precipitate (0·51 g.; 46%) was crystallised from methanol. Recrystallisation from acetic acid, containing a trace of water, gave faintly green, long, rectangular prisms of *2-methyl-1 : 2 : 3 : 4-tetrahydrofluoranthene* (IV), m. p. 89—91° (Found: C, 92·5; H, 7·1. $C_{17}H_{16}$ requires C, 92·7; H, 7·3%). It gave a 2 : 4 : 7-trinitrofluorenone *complex* as orange needles (from acetic acid), m. p. 208—209° (Found: N, 7·8. $C_{17}H_{16},C_{13}H_5O_7N_3$ requires N, 7·8%).

2-Methylfluoranthene (V).—(IV) (0·22 g.), chloranil (0·49 g.), were boiled in xylene (2 ml.). The blood-red solution rapidly deposited pale brown tetrachloroquinol and after 1 hour was pale brown. After cooling, the filtered solution was diluted with ether, extracted with 5% sodium hydroxide solution, washed, and evaporated. The crude product (0·2 g.) crystallised from light petroleum (60—80°) and then from ethanol in pale yellow blades, m. p. 72—75° (Wang, *loc. cit.*, gives m. p. 72—73°) of 2-methylfluoranthene (Found: C, 94·5; H, 5·7. Calc. for $C_{17}H_{12}$: C, 94·4; H, 5·6%). It fluoresces pale green in ultra-violet light. A *complex* with *s*-trinitrobenzene gave canary-yellow needles, m. p. 223—226°, from benzene (Found: C, 64·3; H, 3·5; N, 9·9. $C_{17}H_{12},C_6H_3O_6N_3$ requires C, 64·3; H, 3·5; N, 9·8%).

2 : 4-Dimethylfluoranthene.—4-Keto-2-methyl-1 : 2 : 3 : 4-tetrahydrofluoranthene (III) (2·34 g., 0·01 g. mol.), suspended in anhydrous ether (5 ml.), was added to an ethereal solution of methylmagnesium iodide [from methyl iodide, 1·25 ml. (2·84 g., 0·02 g.-mol.), pure magnesium, 0·48 g. (0·02 g.-atom), and ether, 15 ml.]. (III) dissolved, and a white precipitate then slowly separated. The mixture was kept at the b. p. with stirring for ½ hour, treated with dilute hydrochloric acid, and worked up as usual. The product, *2 : 4-dimethyl-1 : 2(?)-dihydrofluoranthene*, was crystallised from glacial acetic acid (to ensure removal of water) and then from ethanol in thick, diamond-shaped plates, m. p. 98—100° (1·62 g., 70%) (Found: C, 92·9; H, 6·9. $C_{18}H_{16}$ requires C, 93·1; H, 6·9%). Its 2 : 4 : 7-trinitrofluorenone *complex*, prepared in glacial acetic acid, gave orange-coloured rosettes, m. p. 143—146° (softening 140°), from glacial acetic acid (Found: C, 67·9; H, 4·0; N, 7·75. $C_{18}H_{16},C_{13}H_5O_7N_3$ requires C, 68·0; H, 3·9; N, 7·7%). Picric acid and *s*-trinitrobenzene gave scarlet and orange-coloured complexes, respectively, but they could not be isolated free of reactants.

2 : 4-Dimethyl-1 : 2(?)-dihydrofluoranthene (0·464 g.), chloranil (0·492 g.), and xylene (2 ml.) were boiled for ½ hour. Working up as usual gave a reddish-brown powder (0·35 g.) which after recrystallisation from methyl cyanide gave 2 : 4-dimethylfluoranthene as faintly greenish-yellow rectangular prisms (0·23 g., 50%), m. p. 116—117° (softening at 114°) (cf. Forrest and Tucker, *loc. cit.*). It fluoresced greenish-yellow in ultra-violet light (cf. Tucker and Whalley, *loc. cit.*, p. 633). Its identity with 2 : 4-dimethylfluoranthene was established by comparison of the picrates and identity of the *complex* with 2 : 4 : 7-trinitrofluorenone prepared from each. The complex was prepared in glacial acetic acid and crystallised from methyl cyanide in very small orange-red needles, m. p. 200° (Found: C, 67·9; H, 3·7; N, 7·7. $C_{18}H_{16},C_{13}H_5O_7N_3$ requires C, 68·25; H, 3·5; N, 7·7%).

2 : 4-Dimethyl-1 : 2 : 3 : 4-tetrahydrofluoranthene.—2 : 4-Dimethyl-1 : 2(?)-dihydrofluoranthene (0·232 g.) was hydrogenated [Cheronis–Levin 5% Pd–C (0·2 g.)] in ethanol (15 ml.) in ½ hour (23 ml. of H_2 absorbed). The mixture was filtered, the charcoal extracted with boiling ethanol and ether, and the solution evaporated to give, after crystallisation from methanol, *2 : 4-dimethyl-1 : 2 : 3 : 4-tetramethylfluoranthene* as long faintly steel-blue prisms, m. p. 79—81° (0·18 g., 77%) (Found: C, 92·1; H, 7·6. $C_{19}H_{18}$ requires C, 92·3; H, 7·7%). It fluoresces pale blue in ultra-violet light. Its *complex* with

2 : 4 : 7-trinitrofluorenone was unstable in ethanol but gave orange-red prisms from glacial acetic acid : these, however, melted after repeated crystallisation capriciously at 80° or 190° and were obviously the complex with one component or the other predominating. The isomeric 2 : 4-dimethyl-1 : 2 : 3 : 4-tetrahydrofluoranthene (Tucker and Whalley, *loc. cit.*) fluoresces pale violet in ultra-violet light. Repetition of the preparation of this isomer in a mixture of equal parts of acetone and glacial acetic acid indicated that this mixture is slightly preferable to ethanol: the acetone acts as a solvent, no hydrogenation taking place in it alone.

I thank Miss R. H. Kennaway and Mr. J. M. L. Cameron for micro-analytical results.

UNIVERSITY OF GLASGOW. [*Received, April 11th*, 1949.]

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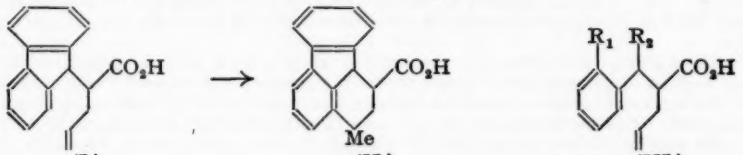
467. *Some Derivatives of* 1-*Benzyl*-n-*but*-3-*ene*-1-*carboxylic Acids.*

By NEIL CAMPBELL and H. WANG.

Three acids related to 1-benzyl-*n*-but-3-ene-1-carboxylic acid have been prepared. Two were found not to undergo ring-closure by the Darzens method (*Compt. rend.*, 1926, **183**, 748, 1110), but the acid (III; R_1 = Me, R_2 = H), although not isolated in a pure state, was cyclised to 4 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid.

1-BENZYL-*n*-BUT-3-ENE-1-CARBOXYLIC ACID is readily converted into a tetralin derivative by sulphuric acid, and the general application of the reaction was realised by Darzens (see Linstead, *Ann. Reports*, 1936, **33**, 326). Since the tetralins are readily dehydrogenated by chloranil to derivatives which are easily decarboxylated, the Darzens method constitutes a good method for synthesising substituted naphthalenes. We have attempted to extend the method by preparing 1-9′-*fluorenyl*-n-*but*-3-*ene*-1-*carboxylic acid* (I) and converting it into 4-methyl-1 : 2 : 3 : 4-tetrahydrofluoranthene-2-carboxylic acid (II). All attempts to effect ring closure of the acid (I), however, were unsuccessful, the products being either unchanged material or sulphonic acids. This failure was quite unexpected since the 1-position in the fluorene molecule, though less susceptible to electrophilic substitution, readily participates in ring closure (see, *e.g.*, France, Tucker, and Forrest, *J.*, 1945, 7, and subsequent papers).



(I.) (II.) (III.)

The simplest explanation would be the formation of a γ-lactone which would be only slowly converted into the cyclic acid (II) (cf. Darzens, *Compt. rend.*, 1930, **190**, 305), but against this is the fact that unchanged material was often obtained under conditions in which 1-benzyl-*n*-but-3-ene-1-carboxylic acid or the corresponding lactone is cyclised. A similar failure in ring closure was obtained with 1-*benzhydryl*-n-*but*-3-*ene*-1-*carboxylic acid* (III; R_1 = H, R_2 = Ph), but 1-2′-methylbenzyl-*n*-but-3-ene-1-carboxylic acid (III; R_1 = Me, R_2 = H) was cyclised to yield finally 1 : 5-dimethylnaphthalene. Attempts to prepare 1-2′-phenylbenzyl-*n*-but-3-ene-1-carboxylic acid (III; R_1 = Ph, R_2 = H) failed.

An attempt was made to cyclise 9-*hydroxy*-9-*epoxyallylfluorene* (cf. Bradsher, *Chem. Reviews*, 1946, **38**, 474), but the only products were resins.

EXPERIMENTAL.

(All analyses were by Drs. Weiler and Strauss, Oxford.)

Preparation of 1-9′-*Fluorenyl*-n-*but*-3-*ene*-1-*carboxylic Acid.*—Fluorenone [2 : 4-*dinitrophenylhydrazone*, orange needles, m. p. 299—301° (Found: N, 15·3. $C_{19}H_{12}O_4N_4$ requires N, 15·55%)] was converted into fluoren-9-ol by the modified method of Werner and Grob (Campbell and Fairfull, this vol., p. 1239), and the fluorenol (25 g.) suspended in glacial acetic acid (150 c.c.). Dry hydrogen bromide was passed through until saturation was reached, and the solution was then heated at its b. p. for 3 minutes with the hydrogen bromide still passing. The cold solution with water gave 9-bromofluorene, crystallising in needles from light petroleum (b. p. 80—100°), m. p. 103—104°; yield, 22 g. (66%). Sodium (1·55 g.) was dissolved in absolute ethanol (45 c.c.), and ethyl allylmalonate (13·2 g.) and then 9-bromofluorene (16·4 g.) were gradually added to the warm solution. The mixture was boiled under reflux until it was no longer alkaline (about 6 hours). Most of the ethanol was removed by distillation, the semi-solid residue shaken with warm water, and the resulting oil extracted with ether. The ethereal layer was

washed 4 times with water, dried (Na_2SO_4), and on evaporation gave crude ethyl α-9-fluorenyl-α-allylmalonate (15 g., 62%), which did not solidify and could not be distilled under reduced pressure without decomposition. The substance was also obtained from allyl bromide and *ethyl 9-fluorenylmalonate*, needles (from aqueous ethanol), m. p. 68—69° (Found: C, 73·95; H, 6·2. $C_{20}H_{20}O_4$ requires C, 74·1; H, 6·2%). The latter compound was prepared but not isolated by Bachmann and Sheehan (*J. Amer. Chem. Soc.*, 1940, **62**, 2687). Ethyl 9-fluorenylallylmalonate (15 g.) was hydrolysed by heating it under reflux for 2 hours with 10% alcoholic sodium hydroxide (50 c.c.). A salt-like solid was obtained which, when dissolved in water and acidified with dilute hydrochloric acid, gave a little effervescence of carbon dioxide and a brown oil which solidified on cooling. The solid was heated at 170—180° until evolution of carbon dioxide ceased. The oil on cooling solidified and when crystallised twice from light petroleum (b. p. 100—120°) gave colourless needles of 1-9′-*fluorenyl*-n-*but*-3-*ene*-1-*carboxylic acid*, m. p. 128—129° (4·25 g., 39%) (Found: C, 81·3; H, 6·3. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%). The acid in ethanol decolorised aqueous potassium permanganate. Efforts to effect ring closure of the acid with concentrated sulphuric or phosphoric acid or both were unsuccessful.

Syntheses of Ethyl α-2-Methylbenzyl-α-allylmalonate and 1 : 5-*Dimethylnaphthalene*.—2-Methylbenzyl bromide (18 g.), ethyl allylmalonate (20 g.), sodium (2·3 g.), and absolute ethanol (40 c.c.) were condensed as above to give *ethyl α-2-methylbenzyl-α-allylmalonate*, b. p. 199—203°/15 mm. (10 g., 34%) (Found: C, 70·15; H, 8·1. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%). The ester (6 g.) was hydrolysed by heating it under reflux with potassium hydroxide (8 g.) in 50% aqueous ethanol (25 c.c.), and the solution was acidified with dilute hydrochloric acid. The mixture was extracted with ether and the ether evaporated; the resulting oil on distillation gave off carbon dioxide and yielded 1-2′-methylbenzyl-*n*-but-3-ene-1-carboxylic acid, b. p. 195—200°/25 mm. This acid could not be prepared in the pure state since distillation was accompanied by slight decarboxylation. The impure acid (6 g.) was shaken with 80% sulphuric acid (18 g.) in the cold, and a solid gradually separated. After 5 hours the solution was neutralised with 12% sodium carbonate and extracted with ether. The aqueous layer on acidification gave 4 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-2-*naphthoic acid*, which was crystallised from 50% ethanol, m. p. 141—142°; yield, 2·0 g. (33%) (Found: C, 76·5; H, 8·0. $C_{13}H_{16}O_2$ requires C, 76·4; H, 7·9%). The acid (1 g.), chloranil (2·5 g.), and xylene (10 c.c.) were heated under reflux for 48 hours, the solution was filtered, and an equal volume of ether added to the filtrate. Extraction with 4% potassium hydroxide followed by acidification yielded a brown product which on repeated extraction with hot water gave 4 : 8-dimethyl-2-naphthoic acid; colourless plates (water), m. p. 186—188° (0·2 g., 20%). The acid was decarboxylated by heating it in an oil-bath at 215—220° with quinoline and copper and subsequent acidification with dilute hydrochloric acid. 1 : 5-Dimethylnaphthalene separated and was crystallised from aqueous ethanol; m. p. 79—80° (lit., 80°); picrate, yellow-orange needles, m. p. 137—138° (lit., 138—139°). An attempt to decarboxylate the dimethyltetrahydronaphthoic acid under the same conditions gave only unchanged acid.

1-*Benzhydryl*-n-*but*-3-*ene*-1-*carboxylic Acid*.—Benzhydryl bromide (22·0 g.), ethyl allylmalonate (18·0 g.), sodium (2·12 g.), and absolute ethanol (60 c.c.) gave *ethyl α-benzhydryl-α-allylmalonate*, a colourless oil, b. p. 237—239°/26 mm. (12·1 g., 37%) (Found: C, 75·85; H, 7·2. $C_{22}H_{26}O_4$ requires C, 75·4; H, 7·15%). The ester was also prepared in 39% yield by condensing allyl bromide with *ethyl benzhydrylmalonate*, which in turn was obtained from benzhydryl bromide and ethyl malonate as an oil, b. p. 233—235°/27 mm., which solidified on storage; m. p. 43—45°; yield, 49% (Found: C, 73·7; H, 6·9. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%). Ethyl benzhydrylmalonate was identified by hydrolysis with 30% sodium hydroxide to the acid which when heated at 170—180° yielded *ββ*-diphenylpropionic acid, m. p. 151—153° (lit., 155°) (anilide, m. p. 175—177°; lit., 177—178°). Ethyl benzhydrylallylmalonate (12 g.) was heated under reflux with 10% sodium hydroxide (50 c.c.) for 3 hours, and on acidification plates of the acid were deposited, m. p. 165—170° with evolution of carbon dioxide. The solid was heated at 180° until evolution of gas was complete, and the resulting oil crystallised from benzene. 1-*Benzhydryl*-n-*but*-3-*ene*-1-*carboxylic acid* separated in prisms, and more was obtained by the addition of light petroleum (b. p. 60—80°); m. p. 156—157°; yield, 1·2 g. (14%) (Found: C, 79·8; H, 6·2. $C_{18}H_{18}O_2$ requires C, 81·15; H, 6·8%). Attempts at ring-closure with concentrated sulphuric acid, phosphoric acid, and mixtures of these acids under a variety of conditions failed, the only products being unchanged material or a charred mass.

Ethyl α-(2-Phenylbenzyl)-α-allylmalonate.—To magnesium (7·5 g.) and dry ether (30 c.c.), *o*-bromotoluene (55 g.) in ether (190 c.c.) was gradually added, the reaction being started by addition of a few drops of methyl iodide. The solution was then heated under reflux for 1½ hours until all the magnesium had dissolved. *cyclo*Hexanone (31 g.) was slowly added, and the solution heated under reflux for 24 hours. The product was worked up in the usual way and 1-*o*-tolyl*cyclo*hexanol was obtained as a liquid, b. p. 154—156°/25 mm. (lit., 149—151°/14 mm.), yield 38 g. (63%). The carbinol (25 g.) was shaken in the cold with 90% formic acid (25 c.c.), and after ½ hour *o*-tolyl*cyclo*hex-1-ene separated in 97% yield. The *cyclo*hexene (20 g.) was heated under reflux for 24 hours with chloranil (57·5 g.) in xylene (150 c.c.). The cold solution was filtered, and an equal volume of ether added to the filtrate, which was then washed twice with 4% potassium hydroxide solution, water, and finally distilled. 2-Methyldiphenyl (12 g., 61·5%) distilled at 134—141°/25 mm. (lit., 130—136°/27 mm.). 2-Methyldiphenyl (3·5 g.) was heated under reflux with *N*-bromosuccinimide (4·5 g.) and carbon tetrachloride (20 c.c.) for 3 hours, and the cold mixture filtered and distilled under reduced pressure. *o*-Phenylbenzyl bromide (4·13 g., 80%) distilled at 168—172°/18 mm. (lit., 166°/12 mm.). The bromide (5·75 g.) was condensed with ethyl allylmalonate (4·60 g.), sodium (0·54 g.), and absolute alcohol (10 c.c.) as above, and gave *ethyl α-2-phenylbenzyl-α-allylmalonate*, b. p. 240—265°/23 mm., which crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 68—69° (3·53 g., 41%) (Found: C, 75·3; H, 7·4. $C_{22}H_{24}O_4$ requires C, 75·4; H, 7·15%). The ester was hydrolysed by 10% alcoholic sodium hydroxide or 50% sulphuric acid, but the resulting oil could be neither solidified nor distilled under reduced pressure without decomposition.

Attempted Preparation of 2-*Methyl*-2′-*chloromethyldiphenyl*.—2 : 2′-Dimethyldiphenyl was prepared by Ullmann's method (*Annalen*, 1904, **332**, 38), but under his conditions, *i.e.*, 230° for 3 hours, very little of the diphenyl compound was obtained from *o*-iodotoluene. At 280° for 6 hours, however, 2 : 2′-

dimethyldiphenyl was obtained as an oil, b. p. 251—258°/747 mm., which solidified in a freezing mixture; m. p. 13—18° (lit., 18°); yield, 62%. Under these conditions *o*-bromotoluene reacted only slightly, even when the time was increased to 15 hours. Attempts to prepare the monochloromethyl compound with sulphuryl chloride and benzoyl peroxide failed.

9-Hydroxy-9-epoxyallylfluorene.—Efforts to prepare 9-hydroxy-9-allylfluorene by the action of allylmagnesium bromide on fluorenone (Backer and Strating, *Rec. Trav. chim.*, 1941, **60**, 391) were unsuccessful, probably owing to the coarse magnesium available which resulted in formation of a considerable quantity of diallyl. With allylmagnesium chloride (Kharasch and Fuch, *J. Org. Chem.*, 1944, **9**, 359), however, 9-hydroxy-9-allylfluorene was obtained in 39% yield as pale yellow prisms (light petroleum), m. p. 114° (lit., 119·5—120°) (Found: C, 86·0; H, 6·3. Calc. for $C_{16}H_{14}O$: C, 86·4; H, 6·35%). 9-Hydroxy-9-allylfluorene (2·22 g.) was dissolved in chloroform containing perbenzoic acid (1·65 g.) and kept in a stoppered bottle in the refrigerator for 24 hours. The solution was shaken with sodium carbonate solution, and the chloroform layer washed with water. The dried chloroform extract on evaporation gave a yellowish solid which was twice purified by dissolving it in the minimum quantity of benzene and adding twice the volume of light petroleum (b. p. 60—80°). *9-Hydroxy-9-epoxyallylfluorene* slowly separated in prisms, m. p. 127—128° (1·82 g., 76·5%) (Found: C, 80·2; H, 6·0. $C_{16}H_{14}O_2$ requires C, 80·6; H, 5·9%). Cyclisation of the epoxide was attempted under conditions similar to those used by Bradsher and Amore (*J. Amer. Chem. Soc.*, 1943, **65**, 2016), but the only product isolated was a black resin.

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UNIVERSITY OF EDINBURGH. [*Received, April 19th*, 1949.]

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468. *Acid-catalysed Alcoholysis. Part II. Aprotic Solvents.*

By M. F. CARROLL.

Methods for the direct measurement of the reaction velocity of acid-catalysed alcoholysis have been devised, permitting a study of the effect of varying the concentration of the reagents.

When octan-1-ol and ethyl acetate in toluene are used at 1 mole per l., the reaction velocity is approximately proportional to the ester and catalyst concentration. It is almost independent of the alcohol concentration over a wide range, but at low alcohol concentrations marked variations are observed. The rate constant increases markedly with decreasing ester concentration.

These findings have been explained on the basis of an extension of the hypothesis advanced in Part I, and it is now suggested that the sharing of the catalyst H^+ ion between the alcohol and the ester gives rise to the above effects. At equimolecular concentrations the distribution of H^+ ion between alcohol and ester is in the approximate ratio 3 : 2.

THE method used in Part I of this work to study acid-catalysed alcoholysis was not sufficiently flexible to permit of accurately comparing the variation of reaction rate with concentration, and the present work describes an attempt to apply more conventional methods. The aim of this investigation and the reasons for preferring the alcoholysis reaction have been described in Part I.

In this reaction, with a suitable choice of reagents, the activities of the ions can be almost identical and the solutions remain homogeneous. The reaction rate can be measured if one of the esters in the system can be removed and the other determined by the ester-value method. For this purpose two procedures were employed. In the first, a low-boiling ester, a high-boiling alcohol, and the catalyst were maintained at a constant temperature in a suitable solvent. After a known interval the solution was transferred to an evaporating vessel and vacuum applied rapidly, the reaction being stopped by the temperature lowering and the removal of the low-boiling ester. The residual high-boiling ester formed was then determined directly by an ester value, allowance being made for the catalyst. The method is fairly general, but the time error is not easily assessed; hence a second method was used as a check. In this method the reaction was stopped by pouring the solution on to a standard sodium hydrogen carbonate solution to remove the catalyst and evaporating the solvent and low-boiling ester as before. Several control tests were necessary for both methods. In addition the uncatalysed reaction was found to be negligible under the conditions of the experiments.

The reagents used were ethyl acetate as low-boiling ester, octan-1-ol as high-boiling alcohol, *m*-xylenesulphonic acid as catalyst, and toluene as solvent.

The method used in Part I had the advantage that the reaction was, in effect, irreversible, whereas in the present work allowance must be made for the reversible reaction. If first-order kinetics are used, the equation for the rate of reaction for any given catalyst concentration is:

$$-\mathrm{d}x/\mathrm{d}t = k_1(a - x) - k_2x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (I)$$

where a is the initial concentration of the low-boiling ester and x the concentration of the high-boiling ester at time t. For the reagents used, the equilibrium constant $K \simeq 1$ and $k_1 \simeq k_2$, and for convenience of calculation the expression

$$k = (2{\cdot}3/2t) \log_{10} a/(a - 2x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

gives a good approximation for small values of x.

The variation of k with time is shown in Table I, which gives the values for the ester and alcohol at molar concentrations in toluene at 25°. The example therein, which is typical of several experiments at different concentrations, shows that k decreases slightly, but not so markedly as in Goldschmidt's study of acid-catalysed esterification (*Z. physikal. Chem.*, 1929, **143**, 139, 278).

TABLE I.

Time, mins.	61	125	227	368
x	0·035	0·068	0·116	0·170
$k \times 10^4$	5·93	5·85	5·81	5·64

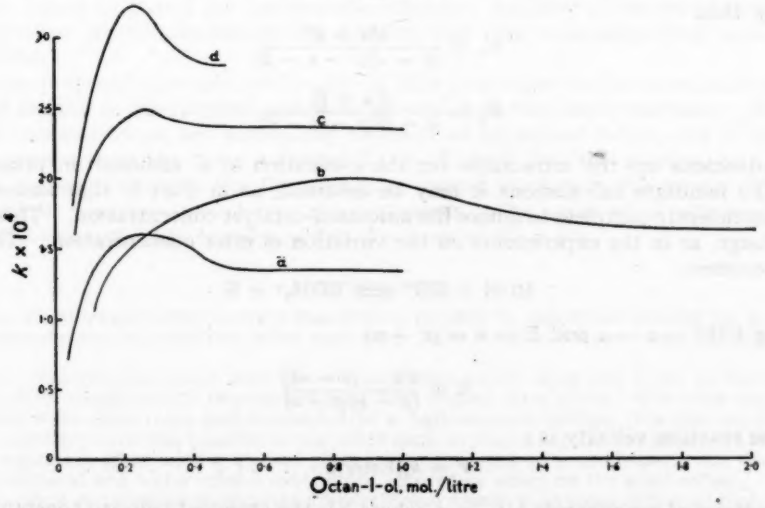
The relative constancy of k as the reaction proceeds has an important bearing on the subsequent work, as it was possible to make only one or two measurements of k at each concentration, and it was assumed that the value of k was independent of the concentrations. This is true for small values of x and in consequence the time intervals were chosen so as to make x as small as possible consistently with a low experimental error.

The effect of varying the ester, alcohol, and catalyst concentration separately was therefore investigated by determining a value of k at varying concentrations of each. Table II shows the values of k for different catalyst concentrations in toluene at 25°. All concentrations are in moles per litre.

TABLE II.

Ester.	Alcohol.	Catalyst.	$k \times 10^4$.	$k/c \times 10^3$.
0·5	0·5	0·0083	1·10	1·32
0·5	0·5	0·010	1·33	1·33
0·5	0·5	0·019	2·38	1·25
0·5	0·5	0·050	5·97	1·20
0·5	0·5	0·100	11·40	1·14
1·0	1·0	0·0167	2·01	1·21
1·0	1·0	0·05	6·15	1·23
1·0	2·0	0·05	5·50	1·10

FIG. 1.



As will be seen from the table there is a small but significant decrease in the value of k/c with increasing catalyst concentration.

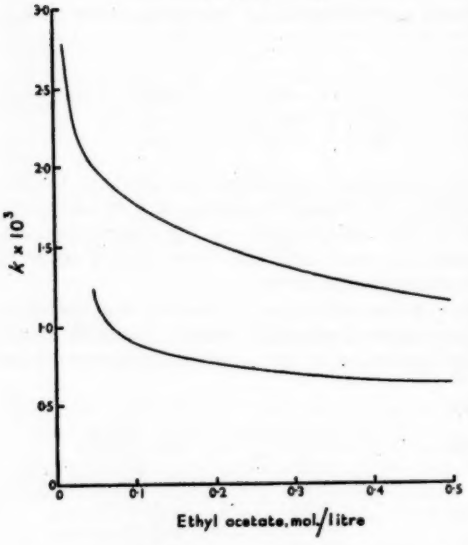
Fig. 1, curves a, b, and c, shows the effect of varying the alcohol concentration in toluene at 25°. Curves a and c are for the first and second methods, respectively, with an ester con-

centration of 0·5 mole per litre, and *b* is for the first method with an ester concentration of 1 mole per litre. In all cases *k* increases slightly as the alcohol concentration decreases, reaches a maximum—which varies with the ester concentration—and then falls rapidly.

In Fig. 2 is plotted the value of *k* against ester concentration with octanol concentration constant at 0·5 mole per litre.

In Part I it was shown that the addition of a polar compound to the reagents in a non-polar solvent reduced the reaction velocity considerably and this was explained by assuming that the catalytic H^+ ion was shared between the reacting alcohol and the added compound. It was also assumed that the ester and solvent took no part in the H^+ ion distribution and that ionisation was substantially complete. Neither assumption is justifiable except in a qualitative sense, but the experimental conditions did not permit of an accurate determination of the effect of varying the concentrations of the reagents. If, however, an added polar substance shares the H^+ ion, the ester reagent must be expected to do so. This view can be shown to be consistent with the results shown in Fig. 2 since, with the decrease in ester concentration, more of the H^+ ion is available for catalysing the alcoholysis.

FIG. 2.



At the beginning of the reaction the catalyst is shared according to the scheme:

$$ROH + HX \rightleftharpoons ROH_2^+ + X^- \quad . \quad (3)$$

$$E + HX \rightleftharpoons EH^+ + X^- \quad . \quad . \quad (4)$$

where ROH, E, and HX refer to the alcohol, ester, and catalyst, respectively. Since measurements were confined to initial changes only, the reverse alcoholysis reaction resulting in the production of the alcohol R'OH and ester E' need not be considered as the total ester + alcohol concentration remains constant and there is no change in the distribution of H^+ ion. If *p*, *e*, and *c* are the initial concentrations of alcohol, ester, and catalyst, and α and β are the concentrations of alkyl oxonium ion and ester ion at equilibrium, then

$$K_1 = \frac{\alpha(\alpha + \beta)}{(p - \alpha)(c - \alpha - \beta)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$K_2 = \frac{\beta(\alpha + \beta)}{(e - \beta)(c - \alpha - \beta)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

These equations are too intractable for the evaluation of α, although in principle this is possible. To facilitate calculations it may be assumed, as in Part I, that ionisation of the catalyst is sufficiently complete to ignore the unionised-catalyst concentration. This is probable when *p* is large, as in the experiments on the variation of ester concentration. The equation therefore becomes:

$$ROH + EH^+ \rightleftharpoons ROH_2^+ + E \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

and putting $EH^+ \doteq c - \alpha$ and $E = e - (c - \alpha)$

$$K = \frac{\alpha[e - (c - \alpha)]}{(p - \alpha)(c - \alpha)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Also, the reaction velocity is:

$$V = k_0[\text{Ester}]\alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

and for any series of experiments $k/k_0 = \alpha$, where *k* is the observed velocity constant as defined by equation (2).

Various values were assigned to *K*, and α was then calculated from the quadratic equation derived from (8). Substituting these values and the results for *k*, the constancy of k_0 could be tested. The best value found for *K* is 1·5, and the calculated values for k_0 are given in Table III.

TABLE III.

Octan-1-ol, 0·5 mole/l. in toluene at 25°.

(*a*) Catalyst = 0·05 mole/l.

Ester, mole/l.	0·5	0·3	0·2	0·1	0·05
$k \times 10^4$	6·32	6·97	7·72	8·8	12·4
$a \times 10^2$	3·2	3·5	3·9	4·4	4·9
$k_0 \times 10^2$	1·98	1·99	1·98	2·0	2·52

(*b*) Catalyst = 0·10 mole/l.

Ester, mole/l.	0·5	0·2	0·1	0·06	0·04	0·03	0·02
$k \times 10^4$	11·4	15·2	18·4	19·5	20·5	21·7	27·4
$a \times 10^2$	6·0	7·8	8·8	9·3	9·5	9·6	9·7
$k_0 \times 10^2$	1·90	1·96	2·09	2·10	2·15	2·26	2·83

The value of k_0 remains constant over a wide range, but there is a marked tendency for it to increase at low values of e. Too much significance should not be attached to this increase because at this low concentration of ester the experimental error is relatively large; thus at $e = 0{\cdot}02$, the total ester corresponds to 4 c.c. of N-sodium hydroxide solution, and the ester formed (*i.e.*, x) is equivalent to 0·8 c.c. after deduction of the relatively large blank (0·4 c.c.). Thus an error of 0·2 c.c. would affect the results at low concentrations seriously, while having little effect at high concentrations. A factor tending to influence the results is the ionisation effect of equation (5) which would make the value of k_0 higher than that calculated from equation (8).

The dielectric effect has been considered in Part I, and in the present work the solvent has been considered only as a diluent which enables the concentrations to be varied. If the substrate is considered as a whole, the dielectric constant increases as the concentration of polar compounds increases, which would give a high value for k on account of the increased ionisation of reaction (3). The effect of the variation of the dielectric constant of the medium on the rate-determining step of the alcoholysis

$$ROH_2^+ + E \rightleftharpoons R'OH_2^+ + E' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

is not so easily decided. It has been sometimes assumed that the variation of the reaction rate of esterification or hydrolysis in polar solvents is entirely a function of the dielectric effect.

In this work the total dielectric effect must be small, since an increase in the concentration of the relatively strongly polar octanol ($\varepsilon = 12{\cdot}6$ at 25°) has a smaller effect than the less polar ethyl acetate ($\varepsilon = 6{\cdot}03$; Krchma and Williams, *J. Amer. Chem. Soc.*, 1927, **49**, 2412). This has also been shown in Part I for the isomeric octanols; addition of the less polar secondary alcohol produces a greater decrease in the reaction rate than a corresponding amount of the primary alcohol.

The scheme proposed in equations (5) and (8) fails to account for the maxima in the curves of Fig. 1 and the fall in the reaction rate with increasing alcohol concentrations. However, at high alcohol concentrations, ion association becomes an important factor, and it follows that k_0 is really greater than the mean value of Table III and that the reaction rate should be measured at a greater dilution, but the advantage gained is offset by the greater experimental error involved in working at such low concentrations. The value of K obtained with the highest reliable value of k still remains within the range of $1{\cdot}5 \pm 0{\cdot}2$.

EXPERIMENTAL.

Materials.—Good-quality ethyl acetate was further purified by fractional distillation, and only the middle fractions of constant refractive index were used. The other materials were purified as described in Part I.

Apparatus.—The reaction tubes were of resistance glass 40 cm. long and 3 cm. in diameter. The vacuum-evaporator consisted of a two-necked flask with ground glass joints. One neck carried a short column packed with glass rings and connected to a high-vacuum system (1·0 mm. of Hg) of high capacity. A capillary tube was inserted in the other neck to ensure regular ebullition. The hydrolysis flask was of resistance glass with a ground glass joint connected to a condenser. All the apparatus was leached with acid and water until a control test showed no effect on the ester value.

Method 1.—Pure *m*-xylenesulphonic acid dihydrate was dissolved in some of the octanol, the solvent added, and water removed by distilling off the solvent–water azeotrope until the distillate was dry. The solution was then made up to the required strength by adding dry toluene. When it was necessary to vary the octanol concentration, only sufficient octanol was used to ensure solution of the catalyst and the requisite alcohol concentration was obtained by adding a 2N-solution of the octanol. A 2N-solution of ethyl acetate was prepared and the strength checked by the ester value. All solutions were made up at 25° and transferred at that temperature. Suitable quantities of reagents were pipetted

into the reaction tube, zero time being taken as the end of the addition when the tubes were shaken to mix the contents. The period of addition was about 30 seconds, and the time error due to mixing was usually less than 1%. After a suitable time, the contents of the tube were poured into the evaporating vessel and the full vacuum applied, the temperature falling rapidly to −10°. When all the solvent had been removed, the residue was washed into the hydrolysis flask with pure ethanol and made up to 50 c.c. An excess of aqueous N-sodium hydroxide was added and the solution heated under gentle reflux for 2 hours. After the solution had been cooled, 100 c.c. of CO_2-free water were added and the whole titrated with standard acid. For small values of x weaker standard solutions were used, *e.g.*, 0·2 N. When the corrections found in the control tests are applied, the value of x is obtained directly from the titration difference. The following control tests were carried out. (i) Ester value on individual reagents—the titre was negligible. (ii) The strength of catalyst solution was determined by titration with standard alkali to bromophenol-blue. (iii) An ester value on the catalyst–octanol solution gave a titre varying with the catalyst concentration and ranged from 0·05 to 0·4 c.c. with N-sodium hydroxide. (iv) The reaction tube was rinsed with water after use, and the solution titrated. This was necessary to ensure that no catalyst had deposited during the reaction. (v) The correction actually applied was the overall result obtained by carrying out the process at zero time, *i.e.*, by applying the vacuum immediately on mixing. The titre obtained which included that due to the catalyst was used as the actual control.

Method 2.—The procedure is the same as in Method 1 except that the reaction is stopped by shaking with standard sodium hydrogen carbonate solution, separating the solvent layer, and removing the solvent and low-boiling ester under vacuum as before. By titrating the aqueous layer with standard acid it is possible to check the amount of catalyst used in each experiment. A correction must be applied to allow for the slight hydrolysis of the ester due to the aqueous hydrogen carbonate solution. This was determined by using known amounts of octyl acetate and noting the amount hydrolysed in the above procedure.

A typical examples of the results obtained by method 2 is given below in Table IV.

TABLE IV.

Ethyl acetate, 0·1 mole; catalyst, 0·004 mole; and octan-1-ol, made up to 200 c.c. with toluene.

Octan-1-ol, mole	0·01	0·02	0·03	0·05	0·06	0·07	0·10	0·20
t, mins.	180	150	150	149	150	150	152	150
0·5N-NaOH, c.c.	5·8	6·4	6·9	7·5	7·3	7·1	6·9	6·6
Correction, c.c.	−0·2	−0·2	−0·2	−0·2	−0·1	−0·1	±0·0	+0·2
$k \times 10^4$	1·60	2·13	2·31	2·52	2·50	2·44	2·39	2·35

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469. *Acid-catalysed Alcoholysis. Part III. Polar Solvents.*

By M. F. CARROLL.

The effect of the addition of polar compounds to the acid-catalysed alcoholysis reaction in toluene has been further studied, and the methods used in Part II have been modified to permit of the use of some polar compounds as solvents.

The reduction of reaction velocity on the addition of polar compounds to the aprotic solvent has been confirmed and explained on the basis of hydrogen ion distribution between ester, alcohol, and added compound.

The great difference in reaction velocity when polar compounds are used as solvents has been shown to be quantitatively related to the proton affinity of the solvent.

IT has been shown in Part I (this vol., p. 557) that the presence of an added polar compound during an acid-catalysed alcoholysis reaction in an inert solvent reduces the reaction velocity considerably. This was ascribed to the sharing of the hydrogen ion between the alcohol and the added polar compound. In Part II (preceding paper) a method was described which enabled the hydrogen ion distribution between the reagent alcohol and ester to be determined by varying the concentrations of the reagents, and it was shown that the equilibrium constant K_E for the reaction

$$R{\cdot}OH + EH^+ \rightleftharpoons R{\cdot}OH_2^+ + E \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where R·OH is octan-1-ol and E is ethyl acetate, is of the order 1·5.

For the alcoholysis reaction the basic velocity constant $-k_0$ was found to be $2{\cdot}0 \times 10^{-3}$ mol.l.$^{-1}$min.$^{-1}$ This constant is defined by the expression

$$V = k[CH_3{\cdot}CO_2Et] = k_0[CH_3{\cdot}CO_2Et]\alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where k is the observed velocity constant and α the alkyloxonium-ion concentration.

Having determined the relative affinity of the alcohol and the ester for the hydrogen ion, it was then possible to calculate the distribution on adding a polar compound S to the system. With the assumption made in Part II, the sytem is defined by equation (1) and the equation

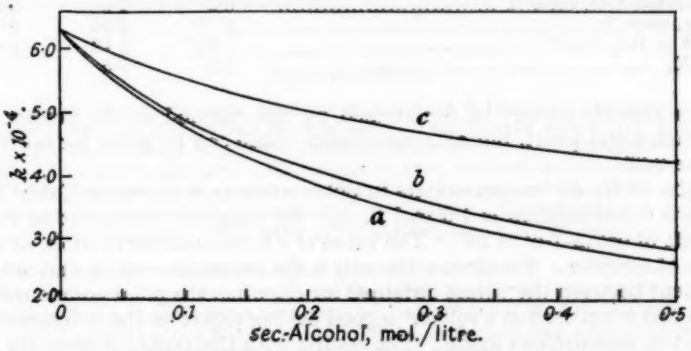
$$S + R{\cdot}OH_2^+ \rightleftharpoons R{\cdot}OH + SH^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

A third relation between E and S is implicit in (1) and (3).

If the alcohol and ester concentrations are large in comparison with the catalyst concentration, the equilibrium constant K_S for reaction (3) is given by

$$K_S = \frac{(p-a)\{c-a(1+e/PK_E)\}}{a\,.\,[s-\{c-a(1+e/PK_E)\}]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where p, e, c, and s are the initial concentrations of the alcohol, ester, catalyst, and added polar compound, respectively. From (2), $\alpha = k/k_0$, and, since K_E and k_0 are known, the value of K_S for any non-esterifiable compound added to the system can be calculated by substituting the observed value of α in (4). If the aprotic solvent can be regarded as a diluent only, on its replacement by a more polar compound, equation (4) should still apply and the value of K_S should be the same. This was found to be substantially true.



The method used for determining the reaction velocity was the same as in Part II when toluene was used, but when acetone was substituted as solvent a modification was necessary. Before evaporation of the solvent and low-boiling ester, toluene was added to facilitate the removal of the ester. In this case the ester is not removed so rapidly, but owing to the lower temperature reached by the evaporation of the acetone under a high vacuum, the reaction is effectively stopped. This source of error is also compensated to some extent, as the reaction velocity is much less in polar solvents and the time interval is consequently greater, so that the time interval error is small and usually less than 1%. With solvents that can be salted out the washing method can be used, provided that an extractive solvent is also used.

The number of polar solvents which can be employed is small and in practice is limited to ethers and ketones, although *tert.*-butanol was also used, as the amount of esterification, if any, is very slight and does not affect the result. This alcohol, acetone, and dioxan were chosen as they are easy to obtain in a very pure condition. These solvents are also not appreciably affected by the catalyst under the conditions of the experiment. In each case tests were made to verify this by examining a solution of the catalyst after a period of storage at room temperatures.

The variation of the observed rate constant k with three added secondary alcohols is shown in the figure. The curves refer to *iso*propanol (*a*), octan-2-ol (*b*), and phenylmethylcarbinol (*c*) at 0·05 mol./l. octan-1-ol and ester, 0·05 mol./l. catalyst, and variable amounts of added secondary alcohol in toluene at 25°. It will be seen that the curve for octan-2-ol is similar to that shown in Part I for the irreversible method.

An example of the constancy of K_S with varying concentrations of added polar compounds is shown in Table III. In this and other cases K_S is fairly constant over a wide range, but at low concentrations, *i.e.*, $<0{\cdot}025$ mol./l. of added polar compound, the experimental error in the evaluation of k is comparable with the expected difference in the rate and reliable results cannot be obtained. In the evaluation of K_S no account has been taken of the contribution to the total ester value owing to the presence of the esterifiable secondary alcohols. As was shown in Part I, this effect is quite small; the actual values are $k/c = 12{\cdot}4 \times 10^{-6}$ and $0{\cdot}8 \times 10^{-6}$ for

octan-1- and -2-ol, respectively. However a slightly increased value of α will be given for a non-volatile alcohol and a decreased value for a volatile one. Hence the recorded value of K_S will be slightly too high for *iso*propanol and too low for octan-2-ol.

For the system, 0·5 mol./l. each of ethyl acetate, octan-1-ol, and added polar compound, and 0·05 mol./l. of catalyst in toluene at 25°, the values of K_S are: *tert.*-butanol 3·8, α-terpineol 2·8, *iso*propanol 2·4, octan-2-ol 2·0, phenylmethylcarbinol 0·76, acetone 0·50, dioxan 0·45. Also, since $K_E = 1·5$, the reference substance, octan-1-ol, is 1·0 and ethyl acetate 0·67. The

TABLE I.

Solvents: (*a*) acetone, (*b*) dioxan, (*c*) *tert.*-butanol.

(*a*) Octan-1-ol, mols./l.	1·0	1·5	2·0
s, mols./l.	10·3	9·2	8·1
$k \times 10^4$, min.$^{-1}$	1·14	1·70	2·46
K_S	0·62	0·64	0·59
(*b*) Octan-1-ol, mols./l.	1·0	1·5	2·0
s, mols./l.	8·75	7·9	6·93
$k \times 10^4$, min.$^{-1}$	1·48	2·06	2·49
K_S	0·58	0·64	0·68
(*c*) Octan-1-ol, mols./l.	0·5	1·0	2·0
s, mols./l.	9·15	8·05	6·35
$k \times 10^5$, min.$^{-1}$	1·63	2·13	4·25
K_S	3·3	5·6	7·0

value of K_S for phenols cannot be determined by this method as the presence of the phenol affects the titration end-point, but an approximate value can be given for *m*-cresol, which from Part I would be 0·33.

The variation of K_S for measurements in polar solvents is shown in Table I. In each case the ethyl acetate concentration is 1·0 mol./l. and the catalyst concentration 0·05 mol./l., with varying amounts of octan-1-ol at 25°. The value of *s* is the number of mols. of solvent required to make up 1 l. of solution. For dioxan the unit is the molecular weight and not the equivalent.

The agreement between the values obtained for K_S when the polar compound is added to the toluene system and when used as a solvent is good having regard to the difference in experimental conditions and the assumptions made. The results with the polar solvents are not so accurate as with the toluene system where the added polar compound concentration can be measured with greater accuracy. The high values for K_S obtained with *tert.*-butanol as solvent are noteworthy and are probably due to increased ion association at the high concentration of octan-1-ol employed.

In contrast to the large reduction in the rate constant by the addition of polar compounds in an aprotic solvent as shown in the figure the reduction is small when polar compounds are added to the polar solvent system. This is shown in Table II, which also summarises the reaction velocities for the alcoholysis reaction in various solvents under the same conditions. Concentrations are 1·0 mol./l. for ethyl acetate, octan-1-ol, and added compound, and 0·05 mol./l. for the catalyst. The temperature was 25° ± 0·1°.

TABLE II.

Solvent.	Added compound.	$10^3 k/c$ & max. deviation from mean.
*iso*Octane	Nil	13·0 ± 0·4
Toluene	Nil	12·4 ± 0·4
Toluene	Octan-2-ol	5·4 ± 0·3
Acetone	Nil	2·28 ± 0·1
Acetone	Octan-2-ol	2·10 ± 0·1
Acetone	*tert.*-Butanol	1·88 ± 0·1
Dioxan	Nil	2·96 ± 0·15
Dioxan	Octan-2-ol	2·86 ± 0·15
Dioxan	*tert.*-Butanol	2·46 ± 0·15
tert.-Butanol	Nil	0·43 ± 0·05

The small but significant difference in the values of k/c for toluene and *iso*octane shows that the former possesses some affinity for the hydrogen ion, and the latter should have been used as solvent, but the solubility of the catalyst is less in *iso*octane and exhibits a tendency to deposit from solution when small concentrations of octanol are used. The assumption that toluene is a

completely aprotic solvent introduces a source of error, but this cannot be accurately determined as the proton affinity is too small significantly to affect the experimental data.

The values of K_S are a measure of the proton affinity or basicity of the added polar compound, and, as stated in previous work, the dielectric constant of the substrate is not an important factor, the results being accounted for on the basis of the hydrogen ion sharing by the polar compounds in the system. Since Part I was accepted for publication, some work has been published (Braude, *J.*, 1948, 1971; Braude and Stern, *ibid.*, pp. 1976, 1982) in which the authors of the third paper have arrived at the same conclusion for an acid-catalysed anionotropic rearrangement, and the present work may be considered as confirmation of their views. In the first paper Braude also measured the acidity function for a group of solvents and concluded that the basicities or proton affinities were in the order water > dioxan > ethanol > acetone. Obviously, water or ethanol cannot be compared directly in the alcoholysis reaction as described in this paper, but if it is assumed that K_S for ethanol is $\simeq 1$, the value for the standard octan-1-ol, then the order is ethanol > acetone > dioxan. Braude, from a consideration of electron availability alone, assumes that the order should be ether > ethanol > acetone, but there are other factors to be taken into account. Whereas in the present work the ionization of the catalyst may be regarded as practically complete owing to the presence of a large concentration of reagents in the otherwise non-ionizing solvents, Braude shows that the ionization of hydrochloric acid in dioxan is small, and the low concentration of reagents that he used would not increase the ionization appreciably.

Experimental.

Materials.—The preparation of most of the materials used has been previously described. The remainder were low-boiling solvents which were selected on account of their original purity. The *tert.*-butanol was crystallised to constant m. p.; the *iso*propanol and dioxan were distilled over sodium, and the acetone was treated with permanganate. All the above were distilled, middle fractions only being used.

Method.—The catalyst solution was made up as follows. The catalyst was dissolved in the octan-1-ol, benzene added, and the water removed by azeotropic distillation. The benzene was completely removed under high vacuum, and the residue was made up to the required dilution with the polar solvent to be used.

When acetone was used as solvent the direct procedure of Part II was applied with the following modification. After applying vacuum to remove the solvent and stop the reaction, 50 c.c. of chilled toluene were added to serve as entrainant for removing the last trace of ethyl acetate.

With dioxan and *tert.*-butanol as solvents, the washing procedure was used with some modification. To stop the reaction, the contents of the reaction tube were poured on to 100 c.c. of toluene and 50 c.c. of a standard sodium hydrogen carbonate solution containing 200 g./l. of sodium chloride, and the mixture shaken vigorously. The aqueous layer was removed, and the top layer shaken with 25 c.c. of 20% brine. The non-aqueous portion was evaporated, and the ester determined as previously described.

The control tests were carried out as described in Part II and applied in the same manner. With acetone and toluene as solvent there is a negative correction, but with dioxan and *tert.*-butanol there is a somewhat large positive correction.

An example of the results obtained and the data employed in calculating K_S is given in the following table where the concentrations are: ethyl acetate and octan-1-ol, 0·5 mol./l., *m*-xylenesulphonic acid, 0·05 mol./l., with varying amounts of octan-2-ol in toluene at 25°. $K_S = 1{\cdot}5$ and $k_0 = 0{\cdot}02$ mol.$^{-1}$l.min.$^{-1}$

Table III.

Octan-2-ol, mols./l.	0	0·025	0·05	0·10	0·25	0·5
N-NaOH, c.c.	8·25	9·1	7·1	6·55	5·25	3·8
Correction, c.c.	−0·4	−0·45	−0·35	−0·30	−0·40	−0·25
t, mins.	135	162	133	136	132	135
$k \times 10^4$	6·32	5·86	5·45	4·83	3·83	2·73
K_S	—	0·81	1·76	1·98	1·95	2·04

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470. *The Action of Selenious Acid on Alkyl Ethers of Phenols.*

By G. V. Boyd, M. Doughty, and J. Kenyon.

In the presence of water selenium dioxide reacts with aryl alkyl ethers to yield the corresponding di-*p*-alkoxyphenyl selenides.

The use of anisole as a solvent for a reaction in which selenium dioxide was being employed as an oxidising agent led us to suspect that interaction between these two compounds was taking place. Accordingly the matter was investigated and the results are now presented.

When anisole is heated at temperatures somewhat below its boiling point with ordinary—*i.e.* not recently resublimed—selenium dioxide a reaction occurs resulting in the separation of water and the development of a red colour. From the reaction mixture di-*p*-methoxyphenyl selenide can be readily isolated.

In marked contrast, when anisole is heated with freshly sublimed selenium dioxide no reaction occurs, even during 20 hours at 130—150° and the selenium dioxide remains largely undissolved. When, however, a few drops of water are added and the mixture reheated reaction soon sets in. Since water is necessary to initiate the reaction it seems likely that the ether is attacked by selenious acid rather than by selenium dioxide. Subsequent experiments indicated that the maximum yield of di-*p*-methoxyphenyl selenide (about 20%) is obtained when the added water amounts to one molecular proportion.

It seems reasonable to suppose that di-*p*-methoxyphenyl selenoxide or di-*p*-methoxyphenylselenium dihydroxide is formed intermedially during the conversion of anisole into di-*p*-methoxyphenyl selenide and to obtain evidence bearing on this view two experiments were performed.

The first one showed that when di-*p*-methoxyphenylselenium dihydroxide in anisole solution was heated at 130—150° for 15 hours only some 10% had been converted into di-*p*-methoxyphenyl selenide. It has to be remembered, however, that the reaction between anisole and selenious acid is a complex one during which selenium is, in all probability, liberated and this suggested the second experiment. This showed that di-*p*-methoxyphenylselenium dihydroxide, dissolved in 50% acetic acid containing in suspension freshly precipitated selenium, heated for 3 hours was converted almost completely into di-*p*-methoxyphenyl selenide—no di-*p*-methoxyphenylselenium dihydroxide was recovered.

In this reaction and in the reactions between selenious acid and other phenolic ethers the selenides formed are always accompanied by red oily by-products of an intractable nature.

By action of selenious acid the following ethers have been converted into the corresponding selenides: phenetole, *o*- and *m*-dimethoxybenzene, 1- and 2-methoxynaphthalenes, and *p*-bromoanisole; *o*-dimethoxybenzene yielded a mixture of the selenide and the diselenide whilst *p*-dimethoxybenzene and diphenyl ether yielded selenium-containing products of high melting points which, owing to difficulties of purification, were not further examined.

Dimethoxyphenyl selenide has been previously prepared by reduction of the dichloride resulting from the action of selenium oxydichloride on anisole (Alquist and Nelson, *J. Amer. Chem. Soc.*, 1931, **53**, 4033) but the position of the selenium atom was left undetermined. That it occupies the *pp'*-position has now been established since diazotised *p*-anisidine is converted by the action of potassium polyselenide into di-*p*-methoxyphenyl selenide identical with that obtained from anisole and selenious acid. It seems probable, therefore, that the selenides obtained by the action of selenious acid on *o*- and *m*-dimethoxybenzenes are bis-3 : 4- and bis-2 : 4-dimethoxyphenyl selenide respectively.

In order to characterise the various selenides the following derivatives were prepared: di-*p*-methoxyphenylselenium dibromide; and di-*p*-methoxyphenylselenium dihydroxide, (*a*) by the action of sodium hydroxide on the dibromide, (*b*) by the action of hydrogen peroxide on the selenide.

The corresponding derivatives of di-*p*-ethoxyphenyl selenide were prepared by the same methods.

The selenide obtained from *o*-dimethoxybenzene does not combine with bromine to yield a stable dibromide but is converted by hydrogen peroxide into the dihydroxide.

Experimental.

The various ethers were purified by shaking them with sodium hydroxide followed by distillation, or recrystallisation; the selenium dioxide was purified by sublimation.

Non-interaction of Anhydrous Selenium Dioxide and Anisole.—A mixture of freshly sublimed selenium dioxide (50 g.) and anisole (125 g.) was stirred and maintained at 130—150° for 20 hours but no reaction occurred. A similar negative result was obtained when dioxan was used as a diluent.

Action of Selenium Dioxide on Anisole in the Presence of Water.—A mixture of selenium dioxide (50 g.), water (8·2 g., 1 mol.), and anisole (125 g., 2·5 mols.) was maintained at 130—150° for 20 hours and the unchanged anisole removed in a current of steam. The semi-solid non-volatile residue was dissolved in ether (Norit), the solution dried, and the solvent removed. The orange solid residue (27 g.; 20%, on selenium dioxide used), after several crystallisations from alcohol, yielded di-*p*-methoxyphenyl selenide as colourless, glistening leaflets (14 g.), m. p. 56·5—58° (Found: C, 57·1; H, 5·0; OMe, 21·0. Calc. for $C_{14}H_{14}O_2Se$: C, 57·3; H, 4·8; OMe, 21·2%).

Di-*p*-methoxyphenyl selenide was obtained by the action of potassium polyselenide on diazotised *p*-anisidine following the procedure given in *Org. Synth.*, 1938, **18**, 28, for the preparation of diphenyl selenide. It was obtained in 10% yield and had m. p. 56—57° alone or when mixed with the selenide prepared from anisole.

In a similar manner diazotised *o*-anisidine and potassium polyselenide yielded *di-o-methoxyphenyl diselenide* in 18% yield. It separated from alcohol in pale yellow needles, m. p. 83—84° (Found: C, 44·9; H, 3·7. $C_{14}H_{14}O_2Se_2$ requires C, 45·2; H, 3·8%).

Di-p-methoxyphenylselenium dibromide. This compound is highly susceptible to moisture and consequently difficult to recrystallise. It is therefore best prepared in dilute solution from which it will separate in a pure crystalline condition. A solution of bromine (3 g.) in carbon disulphide (30 ml.) was added quickly to a solution of the selenide (1·0 g.) in the same solvent (30 ml.). Almost immediately di-*p*-methoxyphenylselenium dibromide separated in theoretical yield in orange-red prismatic rods, m. p. 118—120° (decomp.) (Found: C, 37·0; H, 3·0; Br, 36·6. Calc. for $C_{14}H_{14}O_2SeBr_2$: C, 37·1; H, 3·1; Br, 35·3%).

Di-p-methoxyphenylselenium dihydroxide. (*a*) When di-*p*-methoxyphenylselenium dibromide was triturated with sodium hydroxide solution it became pasty, lost colour, and soon set hard. The resulting dihydroxide separated from alcohol or benzene in colourless needles, m. p. 148° (Found: C, 51·6; H, 4·6. Calc. for $C_{14}H_{16}O_4Se$: C, 51·4; H, 4·9%). (*b*) Di-*p*-methoxyphenyl selenide (3 g.) was triturated with hydrogen peroxide (3 ml.; 30%) and a vigorous reaction set in with evolution of heat. The resulting dihydroxide, after crystallisation, had m. p. 148°, alone or mixed with the compound prepared as under (*a*). It was unchanged after being heated for 10 minutes at 220° (Alquist and Nelson, *loc. cit.*, give m. p. 54° for di-*p*-methoxyphenyl selenide, m. p. 125° for di-*p*-methoxyphenylselenium dibromide, and m. p. 134° for di-*p*-methoxyphenyl selenium dihydroxide).

The Action of Selenious Acid on Various Aryl Ethers.—On phenetole. A mixture of selenium dioxide (20 g.), water (3·2 ml.), and phenetole (55 ml.) after being heated at 120—140° for 20 hours and worked up as previously described yielded 20% of di-*p*-ethoxyphenyl selenide as needles, m. p. 61—62° (Alquist and Nelson, *loc. cit.*, give m. p. 60—62°) (Found: C, 60·3; H, 5·8; OEt, 26·2. Calc. for $C_{16}H_{18}O_2Se$: C, 60·1; H, 5·7; OEt, 28·1%).

Its dibromide formed bright red plates, m. p. 115° (decomp.), and its dihydroxide, prepared either by the action of sodium hydroxide on the dibromide or by the action of hydrogen peroxide on the selenide, formed plates, m. p. 172—173° (Alquist and Nelson, *loc. cit.*, give m. p. 148°) (Found: C, 54·4; H, 5·4. Calc.: C, 54·1; H, 5·7%).

On o-dimethoxybenzene. A mixture of selenium dioxide (10 g.), water (1·8 ml.), and *o*-dimethoxybenzene (25 g.) was heated at 130—150° for 20 hours and yielded a product which on fractional crystallisation from aqueous alcohol was separated into the more soluble *bis*-3 : 4-*dimethoxyphenyl selenide* (1·5 g.) and the less soluble *bis*-3 : 4-*dimethoxyphenyl diselenide* (12·9 g.).

The selenide, which separated as needles, m. p. 101—102·5° (Found: C, 54·1; H, 5·2. $C_{16}H_{18}O_4Se$ requires C, 54·4; H, 5·1%), reacted readily with hydrogen peroxide to give *bis*-3 : 4-*dimethoxyphenylselenium dihydroxide* which crystallised from alcohol in plates, m. p. 170—172° (Found: C, 49·7; H, 4·8. $C_{16}H_{20}O_6Se$ requires C, 49·6; H, 5·2%). The diselenide separated from alcohol in small prisms, m. p. 169—170° (Found: C, 44·9; H, 4·0. $C_{16}H_{18}O_4Se_2$ requires C, 44·5; H, 4·2%).

On m-dimethoxybenzene. This compound, treated as was the *o*-compound, gave *bis*-2 : 4-*dimethoxyphenyl selenide* (yield, 25%) as plates, m. p. 108—110°, from alcohol (Found: C, 54·6; H, 5·2. $C_{16}H_{18}O_4Se$ requires C, 54·4; H, 5·1%). Hydrogen peroxide had no action on this compound; bromine does not combine with it directly to give a coloured addition compound but effects a more complex reaction involving the evolution of hydrogen bromide.

On 1-methoxynaphthalene and 2-methoxynaphthalene. These gave, respectively, *di*-(1-*methoxynaphthyl*) *selenide* (28%) as pale yellow rods, m. p. 137—138°, from alcohol (Found: C, 67·4; H, 4·6. $C_{22}H_{18}O_2Se$ requires C, 67·2; H, 4·6%), and *di*-(2-*methoxynaphthyl*) *selenide* (17%) as colourless needles, m.p. 163°, from acetone–alcohol (Found: C, 66·9; H, 4·9%). Hydrogen peroxide had no effect on these selenides, and combination with bromine yielded oils.

On p-bromoanisole. This gave *di*-(5-*bromo*-2-*methoxyphenyl*) [or *di*-(2-*bromo*-5-*methoxyphenyl*)] *selenide* (22%) as colourless prisms, m. p. 150—151°, from alcohol (Found: C, 37·3; H, 2·9; Br, 35·0. $C_{14}H_{12}O_2Br_2Se$ requires C, 37·3; H, 2·7; Br, 35·4%).

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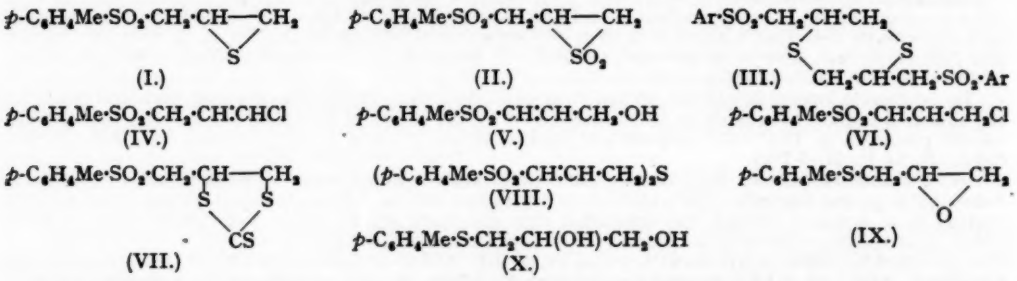
471. *Some Reactions of Arylsulphonylpropane Derivatives.*

By C. C. J. Culvenor, W. Davies, and W. E. Savige.

It is shown that arylsulphonyl-2 : 3-dibromopropanes react (i) with potassium sulphide to form dithians, and not ethylene sulphides (as I) as reported by Troeger and Hornung (*J. pr. Chem.*, 1897, **56**, 445), and (ii) with water under pressure to give, not the glycol claimed by Troeger and his co-workers, but the olefinic alcohol such as 3-p-*tolylsulphonylprop*-2-*en*-1-ol (V). This alcohol may also be prepared from epichlorohydrin and sodium toluenesulphinate or from 1-*chloro*-3-p-*tolylsulphonylpropan*-2-*ol* (as XI) and cold alkali. It dimerises in the presence of hot alkali to the dioxan (XIV) and is converted by phosphorus pentachloride into the corresponding 3-*chloro*-1-p-*tolylsulphonylprop*-1-*ene* (as VI). Reduction of this chloropropene gives tolyl allyl sulphone, and (VI) is isomerised by catalysts into 1-*chloro*-3-p-*tolylsulphonylprop*-1-*ene* (IV), in both cases migration of the double bond occurring. The chloropropenes (VI) and (IV) both add a molecule of alcohol to give the same ethoxy-chloride. Other ready reactions of this sulphonylpropene type of compound, such as fission of the sulphone linkage with alkali, are described.

It is well known that the interaction of alkali-metal sulphides and dihalogenoethanes usually gives sulphur compounds of high molecular weight, together with dithian derivatives. Occasionally the olefin and sulphur are formed (Delèpine and Ville, *Bull. Soc. chim.*, 1920, **27**, 678), but the reported formation of the simple ethylene sulphide is restricted to very few examples, among them being the formation of 3-*p*-tolylsulphonyl-1 : 2-propylene sulphide (I), m. p. 181°, from aqueous potassium sulphide and 1 : 2-dibromo-3-*p*-tolylsulphonylpropane, reported by Troeger and Hornung (*loc. cit.*). It is remarkable also that those authors were able to oxidise their olefinic sulphide with permanganate to the sulphone, for it has been shown (Culvenor, Davies, and Heath, this vol., p. 285) that this is not possible with simple olefin sulphides. A



repetition of their work shows that their " olefinic sulphide," when purified from much amorphous material of high molecular weight, has m. p. 189—190°, and not 181°, and analysis and a molecular-weight determination show it to be 2 : 5-*bis*-p-*tolylsulphonylmethyl*-1 : 4-*dithian* (III; Ar = *p*-C_6H_4Me). The sulphone (m. p. 200°) which they obtained from this must therefore be 2 : 5-*bis*-p-*tolylsulphonylmethyl*-1 : 4-*dithian* 1 : 1 : 4 : 4-*tetraoxide* and not (II). Troeger and Hornung (*loc. cit.*, p. 448) also similarly condensed 1 : 2-dibromo-3-phenylsulphonylpropane with potassium sulphide, and the analysis and molecular weight of the resulting compound, m. p. 157—158°, indicated the formula $C_{18}H_{20}O_5S_4$; the structural formula ascribed to this contained two ethylene sulphide groups. It is now found that the compound (actual m. p. 158—159°) is also a dithian derivative, viz., 2 : 5-*bisphenylsulphonylmethyl*-1 : 4-*dithian* (III; Ar = Ph). It follows that the product (m. p. >230°) which they obtained from its oxidation with permanganate is 2 : 5-*bisphenylsulphonylmethyl*-1 : 4-*dithian* 1 : 1 : 4 : 4-*tetraoxide*.

Unsuccessful efforts have been made to prepare *p*-tolylsulphonylpropylene oxide corresponding to (I), from which (I) might be obtained by the action of thiourea. Oxidation with hydrogen peroxide of 1-p-*tolylthio*-2 : 3-*epoxypropane* (IX), prepared from thiocresol and epichlorohydrin, gives an unidentified oil which is not *p*-tolylsulphonylpropylene oxide. Hydrolysis of (IX) with dilute sulphuric acid forms 3-p-*tolylthiopropane*-1 : 2-*diol* (X), which is also formed from potassium thiocresoxide and glycerol monochlorohydrin.

It has already been shown (Culvenor, Davies, and Heath, this vol., p. 281) that sodium toluene-*p*-sulphinate reacts with simple ethylene oxides to form β-hydroxy-sulphones. Similarly, from propylene oxide 1-p-*tolylsulphonylpropan*-2-*ol* is obtained, oxidisable to *p*-tolylsulphonylacetone, identical with that prepared by Otto and Otto (*J. pr. Chem.*, 1887, **36**, 426) from the sulphinate and bromoacetone. Sodium toluene-*p*-sulphinate and epichlorohydrin give 1-*chloro*-3-p-*tolylsulphonylpropan*-2-*ol* (XI; R = *p*-C_6H_4Me, X = Cl) provided that the alkali formed is

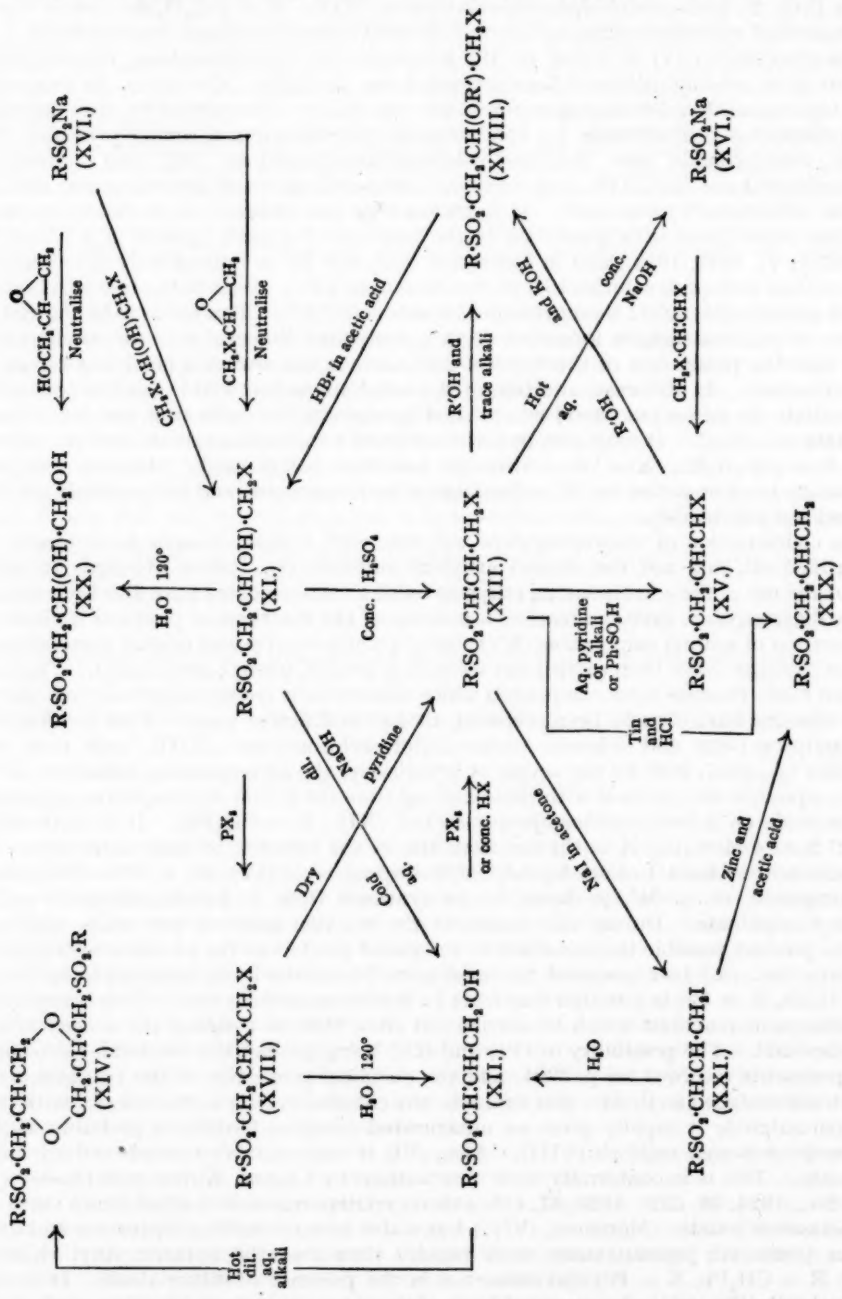
continuously neutralised during the reaction. It has also been prepared from sodium toluene-*p*-sulphinate and glycerol 1 : 3-dichlorohydrin, and is converted by cold dilute alkali into 3-p-*tolylsulphonylprop-2-en-1-ol* (V), m. p. 122°. This product (V) is formed in high yield, along with a little 2 : 5-*bis*-p-*tolylsulphonylmethyldioxan* (XIV; R = *p*-C_6H_4Me), when the toluene-sulphinate and epichlorohydrin are allowed to react without external neutralisation.

The structure of (V) is shown by the formation of a *phenylurethane*, by acetylation with keten to give 1-p-*tolylsulphonyl*-3-*acetoxyprop*-1-*ene* (as XIII; X = OAc), by benzoylation to form 1-p-*tolylsulphonyl*-3-*benzoyloxyprop*-1-*ene* (as XIII; X = O·COPh), and by conversion with phosphorus pentachloride (or concentrated hydrochloric acid under pressure), and phosphorus pentabromide into 3-*chloro*-1-p-*tolylsulphonylprop*-1-*ene* (VI) and 3-*bromo*-1-p-*tolylsulphonylprop*-1-*ene* (as XIII), respectively. Infra-red spectrum determination also indicates that the structure (V) is correct. It is known that the addition of alcohol to αβ-unsaturated sulphones takes place with great ease in the presence of a basic catalyst (*e.g.*, Alexander and McCombie, *J.*, 1931, 1913), and in agreement with this (V) is immediately dimerised by warm dilute sodium hydroxide solution to form the dioxan (as XIV). With potassium ethyl xanthate (V) forms 3-p-*tolylsulphonyl*-1 : 2-*propylene trithiocarbonate* (VII). This seems to be the first recorded instance of trithiocarbonate formation from a compound isomeric with an ethylene oxide and shows that the production of this type of derivative is not always a good test for an ethylene oxide structure. In this case, addition of the xanthate to the double bond produces the same intermediate (or isomer) as would be obtained by opening the oxide ring, and hence the trithiocarbonate is formed. It may also be obtained from potassium xanthate and the chlorohydrin (XI; R = *p*-C_6H_4Me, X = Cl). Although xanthate reacts easily, thiourea and potassium thiocyanate have no action on (V) unless heated under pressure, and the products are then complex and not identifiable.

The condensation of chloropropylene sulphide with sodium toluene-*p*-sulphinate gives an unidentified oil, and not the desired ethylene sulphide (I). Other attempts to prepare (I) without the use of the corresponding ethylene oxide as intermediary have also been unsuccessful.

The diagram on p. 2200 summarises a number of the reactions of products derived from the condensation of sodium sulphinates (XVI) with epichlorohydrin and related compounds. Many of these reactions have been carried out when R is *p*-tolyl, phenyl, and benzyl. The last choice has been made because some compounds which theoretically could be derived from the products of this reaction have already been prepared, though in different ways. Thus 3-chloro-1-benzylsulphonylprop-1-ene and 3-bromo-1-benzylsulphonylprop-1-ene (XIII) have been made by Rothstein (*J.*, 1937, 309) by the action of pyridine on the corresponding dihalides (XVII), and these compounds are identical with those derived from the action of phosphorus pentachloride or pentabromide on 3-*benzylsulphonylprop*-2-*en*-1-*ol* (XII; R = CH_2Ph). It is noteworthy that (XIII; R = *p*-Me·C_6H_4, X = Cl) can isomerise in the presence of basic catalysts or benzenesulphonic acid to form 1-*chloro*-3-p-*tolylsulphonylprop*-1-*ene* (IV), m. p. 74°. The structure of this compound, m. p. 74°, is shown by its synthesis from 1 : 3-dichloropropene and sodium toluene-*p*-sulphinate. During this synthesis the reaction mixture was made faintly acid in order to prevent possible isomerisation of the initial product in the presence of traces of alkali. Rothstein (*loc. cit.*) had prepared the analogous 1-bromo-3-benzylsulphonylprop-1-ene (XV; R = CH_2Ph, X = Br) in a similar way from 1 : 3-dibromopropene and sodium benzylsulphinate, and subsequent reactions which he carried out show that he assigned the correct structure to this compound. The possibility of (VI) and (IV) being geometrical isomerides is negatived by the experiments recorded on p. 2204, and the chemical properties of the two isomers support the formulæ assigned to them. For example, the chlorine in (VI) is reactive, for with potassium hydrogen sulphide it rapidly gives an unsaturated compound which is probably *di*-(3-p-*tolylsulphonylprop*-2-*enyl*) *sulphide* (VIII). Also, (VI) is very reactive towards sodium iodide, but (IV) is not. This is in conformity with observations by Conant, Kirner, and Hussey (*J. Amer. Chem. Soc.*, 1924, **46**, 232; 1925, **47**, 476, 488) on relative reactivities of allyl and vinyl chlorides with potassium iodide. Moreover, (VI) is less stable towards sodium hydroxide and decolorises aqueous potassium permanganate more rapidly than does the isomeric vinyl chloride (IV). (XIII; R = CH_2Ph, X = Br) also isomerises in the presence of dilute alkali. It is surprising that Rothstein (*loc. cit.*), who prepared both of these benzyl isomers by other methods, did not attempt to bring about this interconversion. He had, however, previously found (*J.*, 1934, 684) that no interconversion between the halogen-free benzyl-1- and -2-propenyl sulphones, $CH_2Ph·SO_2·CH{:}CHMe$ and $CH_2Ph·SO_2·CH_2·CH{:}CH_2$, could be effected. In the presence of alkali, the latter compound reacted with alcohol to form the β-alkoxy-derivative. (VI) and (IV) react with alcoholic alkali in the same way, very mild conditions being required, but alkali

with increasing concentration and temperature will convert (VI) into the dioxan (as XIV), or finally bring about fission of the sulphone linkage to form sodium toluene-*p*-sulphinate. The isomeric change in alkali is an example of three-carbon prototropy, similar to that encountered



by Rothstein (*J.*, 1937, 309) in certain disulphones, and also to that described by Connor (Gilman "Organic Chemistry," 1943, Wiley, p. 876) with respect to certain cyclic sulphones. In regard to the latter, Boëseken and van Zuydewijn (*Proc. Acad. Sci. Amsterdam*, 1937, **40**, 23; *Chem. Abs.*, 1937, **31**, 4953) found that cyclic isoprene sulphones with alkali gave a mixture of isomers, the main one of which had the double bond in the αβ-position to the sulphonyl group.

With unsaturated monosulphones, some added factor, such as existence of a ring, whereby the electron-attracting effect of the sulphonyl group is magnified, is apparently necessary to bring about this allylic rearrangement. It is noteworthy that in the present investigation the effect of alkali on (VI) is to produce (IV), in which the double bond is in the $\beta\gamma$-position. The presence of the halogen may be responsible for this isomerism in this acyclic type of monosulphone, and the $\beta\gamma$-position of the double bond may be due to the $(+T)$ or electromeric effect of the halogen atom (compare Baker, " Tautomerism," 1934, Routledge, pp. 20, 29, 87, 88). However, the rôle of benzenesulphonic acid, which has the same effect as alkali, is not understood, as both isomers are stable to hydrochloric, acetic, and sulphuric acid. Another phenomenon is the " double-bond migration," which occurs also during reduction of (XIII; X = Br or I) with zinc and acetic acid, or of (XIII; R = Cl) with tin and hydrochloric acid, the corresponding allyl sulphone being obtained in each case. This rearrangement possibly occurs in the unstable transition state during the replacement of halogen by hydrogen, *e.g.*,

$$\text{(XIII)} \xrightarrow{H} \text{R·SO}_2\text{·CH}_2\text{·CH·CH}_2\text{X} \xrightarrow{H} \text{(XIX)} + \text{HX}$$

To throw more light on the production of the olefinic alcohols from epichlorohydrin, the glycol, 3-p-*tolylsulphonylpropane*-1 : 2-*diol* (XX; R = *p*-C_6H_4Me), was prepared. Troeger and Hinze (*J. pr. Chem.*, 1897, **55**, 213) claimed to have obtained this compound as plates, m. p. 93—95°, insoluble in cold water, by heating 1 : 2-dibromo-3-(*p*-tolylsulphonyl)propane (XVII; R = *p*-C_6H_4Me, X = Br) with water under pressure. A repetition of this reaction has yielded only the olefinic alcohol (V), which has m. p. 122° but, if incompletely dried, melts partially in the range 90—95°. Since the glycol as prepared below has m. p. 74—75°, Troeger and Hinze's product was probably a moist sample of (V). It is easy to overlook the glycol, which tends to retain water, in which it is very soluble, and it is initially difficult to obtain it crystalline except from benzene in the presence of dehydrating agents. On the other hand, the olefinic alcohol is sparingly soluble in cold water. Their work was possibly influenced by the earlier reported conversion under similar conditions of 1 : 2-dibromo-3-phenylsulphonylpropane into 3-phenylsulphonylpropane-1 : 2-diol (XX; R = Ph) by Otto (*Annalen*, 1894, **283**, 189), who also prepared from this product a derivative, m. p. 86—87°, which he regarded as the dibenzoate. However, it was noticed that his supposed glycol had the same physical properties as 3-*phenylsulphonylprop*-2-*en*-1-*ol* (XII; R = Ph), with which, on repetition of the reaction, the product was found to be identical. It was also found that Otto had miscalculated the theoretical analytical data for the " dibenzoate," of which his analysis agreed more closely with the olefinic monobenzoate (XIII; R = Ph, X = OBz). Otto stated that the " glycol " did not react with benzoyl chloride even at 140° and converted it first into the sodium derivative, but it is now found that the alcohol (XII; R = Ph) reacts directly with benzoyl chloride at 100° to form 1-*phenylsulphonyl*-3-*benzoyloxyprop*-1-*ene*, which has the same physical properties as the reported " dibenzoate." Another case of glycol formation, from the reaction of 1 : 2-dibromo-3-benzylsulphonylpropane (XVII; R = CH_2Ph, X = Br) with water under pressure, has been claimed by van Zuydewijn (*Rec. Trav. chim.*, 1938, **57**, 455), who analysed his compound for sulphur only. Once again, it is now found that the product is the olefinic alcohol (XII; R = CH_2Ph), which has essentially the same physical properties (including low solubility in water) as the compound recorded by van Zuydewijn. Furthermore, Troeger and Hinze (*loc. cit.*) and Troeger and Artmann (*J. pr. Chem.*, 1896, **53**, 467) found that the 1 : 2-dibromo-3-α- and -β-naphthylsulphonylpropane (XVII; R = $C_{10}H_7$, X = Br), in the same way, gave compounds, m. p. 127° and 167°, respectively, which analysed correctly for the corresponding ethylene oxides, although these structures were only tentatively given, and they are listed as ethylene oxides in Beilstein (Vol. VI, pp. 622, 658) with a mark of interrogation.

It is now clear by analogy that the compounds are actually 3-α- and -β-*naphthylsulphonylprop*-2-*en*-1-*ol*. Similarly, the two " naphthylsulphonylpropylene sulphides," formed from the same $\beta\gamma$-dibromo-derivatives and potassium sulphide, cannot have the three-membered sulphide ring. These amorphous substances are undoubtedly of high molecular weight and impure. From the present work, there can be no doubt that all the dibromo-sulphones of the type (XVII; R = Ar) are converted by water at high temperatures, not into the ethylene oxide, but into the isomeric unsaturated alcohol, though small amounts of the soluble glycol are not necessarily precluded.

During the study of the mechanism of formation of the unsaturated alcohol (XII; R = *p*-C_6H_4Me), the corresponding glycol (which gives the dibenzoate, 1-p-*tolylsulphonyl*-2 : 3-*dibenzoyloxypropane*), has been made by the oxidation of the sulphide glycol (X) as well as by the methods shown in the diagram. Neither the glycol nor the chlorohydrin (XI), from which it

can be derived, can be an intermediate in the conversion of the dihalide (XVII) into (XII), though it has not been proved that the reaction may not proceed through the unknown isomeric chlorohydrin or the unsaturated chloride (XIII). The surprising ease of the conversion of the chlorohydrin (XI) into the unsaturated alcohol may indicate that the oxide is easily formed but quickly isomerises to (XII) This has some analogy with the formation from epichlorohydrin and sodium acetylide of pent-2-en-4-yn-1-ol, $HC{:}C{\cdot}CH{:}CH{\cdot}CH_2{\cdot}OH$, and the ready conversion of 3-phenylpropylene oxide into cinnamyl alcohol, which it has been suggested may be " brought about by the tendency to form conjugated vinylacetylene and styrene systems respectively " (Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1584).

Experimental.

Preparation of 2 : 5-*Bisarylsulphonylmethyl*-1 : 4-*dithians* (III).—Phenyl allyl sulphone, b. p. 140—145°/0·7 mm., was made from aqueous alcoholic sodium benzenesulphinate and allyl bromide after Otto (*Annalen*, 1894, **283**, 184) who records it only as an oil. During its conversion by bromine in carbon tetrachloride into 1 : 2-dibromo-3-phenylsulphonylpropane, some hydrogen bromide was evolved. A much better yield (92%) of the dibromo-compound was obtained by carrying out the bromination of the allyl sulphone in aqueous suspension (Otto, *loc. cit.*).

2 : 5-*Bisphenylsulphonylmethyl*-1 : 4-*dithian* (III; Ar = Ph). 1 : 2-Dibromo-3-phenylsulphonylpropane (1·1 g.) was dissolved in absolute alcohol (5 ml.) at about 35° and stirred vigorously while a solution of sodium sulphide crystals (1·2 g.) in water (1½ ml.) was added. After 2 hours' stirring, the mixture was kept overnight, and the white powder which separated was filtered off and crystallised from alcohol, giving the *dithian* as glistening needles, m. p. 157—158° (Found: C, 50·6, 50·7; H, 4·9, 5·0. $C_{18}H_{20}O_4S_4$ requires C, 50·6; H, 4·7%). No red coloration appeared at the onset of the reaction as reported by Troeger and Hornung (who used potassium sulphide).

2 : 5-*Bis*-p-*tolylsulphonylmethyl*-1 : 4-*dithian* (III; Ar = *p*-C_6H_4Me). The corresponding dibromopropane (1 g.) and sodium sulphide (1 g.), when brought into reaction as above and kept at 34° for 2 days, yielded the *dithian* (0·3 g.), which formed clusters of minute needles, m. p. 189—190°, after repeated recrystallisation from alcohol [Found: C, 52·3; H, 5·3; *M* (Rast), 473, 476. $C_{20}H_{24}O_4S_4$ requires C, 52·6; H, 5·25%; *M*, 456].

*Derivatives of Thio-*p*-cresol.*—1-p-*Tolylthio*-2 : 3-*epoxypropane* (IX). Epichlorohydrin (9·3 g.) was added slowly to a stirred solution of thiocresol (12·4 g.) and potassium hydroxide (5·6 g.) in water (75 ml.) and alcohol (75 ml.), and the stirring continued for 2 hours before dilution with water and extraction with chloroform. Distillation gave 1-p-*tolylthio*-2 : 3-*epoxypropane* (14·2 g.), b. p. 107·5°/0·2 mm. (Found: C, 66·45; H, 6·4. $C_{10}H_{12}OS$ requires C, 66·7; H, 6·65%).

3-p-*Tolylthiopropane*-1 : 2-*diol* (X) was obtained when the oxide (IX) was heated under reflux for 2 hours with dilute sulphuric acid, and the aqueous layer decanted from a little oil and cooled. Recrystallisation from benzene–light petroleum gave plates, m. p. 58° (Found: C, 61·0; H, 7·4. $C_{10}H_{14}O_2S$ requires C, 60·8; H, 7·1%). (X) was also obtained by shaking a mixture of glycerol monochlorohydrin (11·1 g.), thiocresol (12·4 g.), and potassium hydroxide (5·6 g.) in water (50 ml.) and alcohol (10 ml.) for 1 hour at room temperature and 1 hour on the water-bath, and then extracting it with chloroform (yield, 14·1 g.).

The *diacetyl* derivative, b. p. 166°/0·3 mm., was obtained by heating the glycol (X) with acetic anhydride at 100° for 5 hours and distilling the product (Found: C, 60·1; H, 6·6. $C_{14}H_{18}O_4S$ requires C, 60·1; H, 6·4%).

Oxidation of (IX). The oxide (IX) (5·4 g.) and 30% hydrogen peroxide (10 ml.) were dissolved in acetone (25 ml.), and a little solid barium carbonate added (to neutralize an acid stabilising agent in the peroxide). After 9 days at 34°, the acetone was removed on a water-bath, water added, and products were extracted with chloroform. Distillation gave an unidentified oil (3·9 g.), b. p. 157°/0·2 mm. (Found: C, 64·8; H, 6·3%), and a higher-boiling residue decomposed. The oil was apparently unaffected by heating it with sulphuric acid or alkali.

Reactions of Some Tolylsulphonylpropane Derivatives.

1-*Chloro*-3-p-*tolylsulphonylpropan*-2-*ol* (XI; R = *p*-C_6H_4Me, X = Cl).—Sodium toluene-*p*-sulphinate (8·9 g.) and glycerol dichlorohydrin (6·4 g.) were heated under reflux in aqueous alcohol (50 ml.) for 36 hours, the alcohol removed, and the dried benzene extract distilled *in vacuo* to remove unchanged chlorohydrin. The residue, crystallised from benzene, gave the new *chlorohydrin* (XI) (5·1 g.) as small colourless needles, m. p. 84° (Found: C, 48·35; H, 5·5. $C_{10}H_{13}O_3SCl$ requires C, 48·3; H, 5·25%). On warming (XI) with excess of phosphorus pentachloride on the water-bath for 15 minutes, and pouring into water, 1 : 2-dichloro-*p*-tolylsulphonylpropane (XVII; R = *p*-C_6H_4Me, X = Cl) was obtained in good yield. Recrystallisation from benzene–light petroleum gave m. p. 66—69°, which was not depressed on admixture with a specimen, m. p. 70—72°, prepared by treating a solution of tolyl allyl sulphone in carbon tetrachloride with chlorine according to Troeger and Hinze (*J. pr. Chem.*, 1897, **55**, 204).

3-p-*Tolylsulphonylprop*-2-*en*-1-*ol* (V).—(*a*) The chlorohydrin (XI) (1·5 g.) was powdered and stirred for 1½ hours at room temperature with 3% aqueous sodium hydroxide (15 ml.). The *alcohol* (V) (1·2 g.) separated and was crystallised from water (plates or long needles) and from benzene (plates); m. p. 122°. It was also formed on heating the chlorohydrin under reflux with potassium carbonate in aqueous alcohol for 8 minutes [Found: C, 56·9; H, 5·75; *M* (Rast), 216. $C_{10}H_{12}O_3S$ requires C, 56·6; H, 5·65%; *M*, 212].

(*b*) Epichlorohydrin (4·6 g.) and sodium toluene-*p*-sulphinate (8·9 g.) in water (60 ml.) and alcohol (10 ml.) rapidly became alkaline on admixture. The solution was kept at 32° for 24 hours and gave a semi-solid mass of white plates (9·5 g., 90%) which were identified by mixed m. p. (122°) with the product from the chlorohydrin (XI) and alkali. The crude alcohol (XIV; R = *p*-C_6H_4Me) contained a

trace of the dioxan; m. p. 258°. To isolate the intermediate chlorohydrin (XI), the mixture of toluene-sulphinate and epichlorohydrin with phenolphthalein was warmed, and continuously neutralised by titration with 2N-sulphuric acid. After ½ hour, the rate of production of alkali was extremely slow and the reaction practically complete. Cooling produced an oil, which after extraction with chloroform yielded a solid which crystallised from benzene to give (V) (0·8 g.). Concentration of the mother-liquor produced crystals (1·5 g., 25%), m. p. 75—76°, of the chlorohydrin (XI) (above).

The infra-red spectrum of (V) showed a band at 3520 cm.$^{-1}$ due to free OH and a small band at 1634 cm.$^{-1}$ which is probably due to C=C, but may be a vibration frequency of the benzene ring.

Action of Water on 1 : 2-*Dibromo*-3-p-*tolylsulphonylpropane*.—In an attempt to repeat Troeger and Hinze's preparation of the supposed glycol, m. p. 93—95°, the dibromide was heated in a sealed tube with water for (*a*) 17 hours at 120°, (*b*) 48 hours at 110—120°, (*c*) 17 hours at 140—190°. In each case, the product crystallised from water in plates, m. p. between 115° and 120°, and was identified by mixed m. p. with the alcohol (V). The dibromide was unaffected by being heated under reflux with water at ordinary pressure for 12 hours.

Other Reactions for the Preparation of (I).—Chloropropylene sulphide (5 g.) and alcohol (50 ml.) were added to a neutralised and filtered solution of sodium toluene-*p*-sulphinate (10 g.) in water (40 ml.), and the mixture was kept for 3 days at room temperature. The reaction mixture, which did not become alkaline at any stage, was diluted with water and extracted with chloroform. The extract yielded an oil (2·5 g.), b. p. 110—113°/0·3 mm., and a large residue which decomposed on further heating. The oil (Found: C, 57·5; H, 5·35; S, 18·5%) was halogen-free and partly solidified on storage [$C_{10}H_{12}O_3S_2$ (I) requires C, 52·65; H, 5·25; S 21·05%]. It was expected that the thioacetic acid would add to the olefinic chloride (VI) and that the product on acid hydrolysis would yield the 3-chloro-2-mercapto-derivative and thence (I). Thioacetic acid, however, did not combine with this chloride or with the isomeric 1-chloro-3-*p*-tolylsulphonylprop-1-ene (IV) (see p. 2204).

1-p-*Tolylsulphonylpropan*-2-*ol*.—Propylene oxide (3·5 g.) and sodium toluene-*p*-sulphinate (10 g.) in water (60 ml.) were kept at 32° for 20 hours and the alkali thus formed was neutralised with 2N-sulphuric acid (20 ml.; theory, 28 ml.) before the solution was heated on a water-bath to ensure completion of the reaction. On cooling, 1-p-*tolylsulphonylpropan*-2-*ol* (4·8 g.) separated; from benzene it forms needles, m. p. 77—78° (Found: S, 14·8. $C_{10}H_{14}O_3S$ requires S, 14·95%). When it was boiled for 5 minutes with dilute sodium dichromate and sulphuric acid, a solid was obtained which crystallised from benzene and light petroleum in needles, m. p. 50—51°, before and after admixture with tolyl-*p*-sulphonylacetone made from bromoacetone (after Otto and Otto, *loc. cit.*).

Reactions of 3-p-*Tolylsulphonylprop*-2-*en*-1-*ol* (V).—2 : 5-*Bis*-p-*tolylsulphonylmethyldioxan* (XIV) was immediately formed as a copious precipitate of glistening plates when (V) was warmed with very dilute sodium hydroxide. Though sparingly soluble, it crystallises from alcohol or acetone in plates or needles, m. p. 258° (Found: C, 56·5; H, 5·7. $C_{20}H_{24}O_6S_2$ requires C, 56·6; H, 5·7%). It was also formed on heating aqueous potassium carbonate under reflux with (V), on which aqueous pyridine had no effect, but hot concentrated sodium hydroxide in alcoholic solution gave sodium toluene-*p*-sulphinate.

p-*Tolylsulphonylpropylene trithiocarbonate* (VII) was obtained by heating (V) (0·25 g.) or (XI; R = *p*-C_6H_4Me, X = Cl) (0·5 g.) under reflux for 40 minutes with a xanthate solution prepared from potassium hydroxide (0·35 g.) and carbon disulphide (0·5 g.) in alcohol (10 ml.). Readily soluble in benzene and chloroform, less so in alcohol, it forms from the latter solvent a microcrystalline powder, m. p. 128° (Found: C, 42·9; H, 4·2. $C_{11}H_{12}O_2S_4$ requires C, 43·4; H, 4·0%).

3-p-*Tolylsulphonylprop*-2-*enyl carbanilate* (1·3 g.) resulted when phenyl *iso*cyanate (0·7 g.) and (V) (1·06 g.) were heated in benzene (10 ml.) in a sealed tube at 100° for 3½ hours, and the product precipitated with light petroleum. From ether–light petroleum, it forms long needles, m. p. 104—105° (Found: C, 62·0; H, 5·4; N, 4·2. $C_{17}H_{17}O_4NS$ requires C, 61·6; H, 5·15; N, 4·2%).

1-p-*Tolylsulphonyl*-3-*acetoxyprop*-1-*ene* (XIII; R = *p*-C_6H_4Me, X = OAc) was best obtained by dissolving (V) in excess of acetyl chloride, heating the solution at 50° for 2½ hours, evaporating off the excess of acetyl chloride, and rubbing the residue with water. Though very difficult to crystallise from the usual solvents, it formed long, massive prisms (up to 1 inch long), m. p. 50—51°, when crystallised from ether–light petroleum by slow evaporation of the ether (Found: C, 56·6; H, 5·6; S, 12·7. $C_{12}H_{14}O_4S$ requires C, 56·7; H, 5·5; S, 12·6%). The product obtained from (V) by heating it with acetic anhydride at 100° for 3 hours or with acetic acid for 18 hours, or passing an excess of keten through a solution in dry acetone, was identified with this acetate by mixed m. p. The acetate was completely hydrolysed to (V) by heating it under reflux with 2N-sulphuric acid for 20 minutes or by shaking it in ethereal solution with an equimolecular amount of aqueous sodium hydroxide for 18 hours.

The corresponding benzoate, 1-p-*tolylsulphonyl*-3-*benzoyloxyprop*-1-*ene*, was formed when (V) was heated in excess of benzoyl chloride at 100° for 3½ hours and the excess of halide removed by heating with sufficient dilute sodium hydroxide. Recrystallisation from alcohol gave long needles, m. p. 95° (Found: C, 64·8; H, 5·1. $C_{17}H_{16}O_4S$ requires C, 64·5; H, 5·05%).

3-*Bromo*-1-p-*tolylsulphonylprop*-1-*ene* (XIII; R = *p*-C_6H_4Me, X = Br) was obtained when (V) (4 g.) and phosphorus pentabromide (10 g.) were ground together, warmed for a few minutes, and poured into water (yield: 5·2 g., 100%). Recrystallisation from light petroleum and a little benzene gave needles, m. p. 65—66° (Found: C, 43·8; H, 4·1. $C_{10}H_{11}O_2SBr$ requires C, 43·6; H, 4·0%).

3-*Chloro*-1-p-*tolylsulphonylprop*-1-*ene* (VI) was obtained when the alcohol (V) (5·9 g.) and phosphorus pentachloride (6·3 g.) were mixed, and warmed for a few minutes after the main reaction had subsided, the product being separated by extraction with ether and allowing the solvent to evaporate off at room temperature. Recrystallisation from light petroleum and a little benzene gave plates, m. p. 58° (Found: C, 51·85; H, 5·2. $C_{10}H_{11}O_2SCl$ requires C, 52·05; H, 4·8%). The propene (VI) was also obtained on treatment of (V) with excess of concentrated hydrochloric acid for 23 hours in a sealed tube at 120°, though not at 100° at ordinary pressure for 1 hour; it was also formed by dehydrating the chlorohydrin (XI) with excess of concentrated sulphuric acid at 100° for 2 hours, though not with boiling 70% sulphuric acid. An emulsion of (VI) with cold water instantly decolorised aqueous potassium permanganate but not bromine water. Reduction with tin and hydrochloric acid gave *p*-tolyl allyl sulphone, identified

by m. p. and mixed m. p. (VI) is essentially unchanged at 70° with excess of 70% sulphuric acid, or at 60° with concentrated sulphuric acid, although dissolution rapidly occurs. When 0·2 g. is heated on the water-bath for 1 hour with 4 ml. of 20% potassium hydroxide, cooled, and neutralised, a small amount of unidentified product, m. p. *ca.* 200°, probably the dioxan (XIV), is obtained. Acidification of the filtrate gave toluene-*p*-sulphinic acid, m. p. and mixed m. p. 89—90°. This is obtained in better yield by using 40% alkali.

The propene (VI) (0·2 g.) was dissolved in aqueous alcohol (2 ml.), and the solution exposed, in a silica tube, to direct sunlight for 48 hours. On evaporation of the solvent, little change in m. p. (or mixed m. p.) had occurred. On use of light petroleum as solvent (and a few drops of benzene) and increase in the time of exposure to 100 hours, similar results were obtained.

When (VI) (0·2 g.) was heated under reflux in a solution of light petroleum (20 ml.) containing a trace of iodine, and the solvent allowed to evaporate after 5 hours, (VI) was recovered, m. p. 56—57°.

1-*Chloro*-3-p-*tolylsulphonyl*-2-*ethoxypropane* (as XVIII) was formed when (VI) and 5% of its weight of potassium hydroxide were kept for 2 hours in ethanol solution at 50°. Recrystallisation from benzene–light petroleum gave large cubes, m. p. 79° (Found: C, 52·3; H, 6·35; OEt, 16·75; S, 12·2. $C_{12}H_{17}O_3SCl$ requires C, 52·1; H, 6·15; OEt, 16·3; S, 11·6%). On treating (VI) with a 20% solution of potassium hydroxide in aqueous alkali at 35°, the dioxan (as XIV) was obtained in small yield, together with an unidentified compound, probably 1-*p*-tolylsulphonyl-2 : 3-diethoxypropane, m. p. 40—41°, which was halogen-free and did not decolorise aqueous permanganate. (XVIII; X = Cl) gave a 10% yield of the alcohol (V) when heated under reflux with hydriodic acid in glacial acetic acid, but when 0·2 g. was dissolved in glacial acetic acid (2 ml.), 60% hydrobromic acid (1 ml.) added, and the mixture heated under reflux for 3 hours, the chlorohydrin (XI), identified by mixed m. p., was obtained, *i.e.*, normal de-ethylation had occurred.

Di-(3-p-*tolylsulphonylprop*-2-*enyl*) *sulphide* (VIII) was obtained when the chloride (VI) (1·38 g.) in alcohol (6 ml.) was shaken with a solution of potassium hydrogen sulphide, prepared by saturating the hydroxide (0·28 g.) in ethanol (5 ml.) with hydrogen sulphide at 0°. The product, collected after 15 minutes, crystallised from alcohol in thick needles, m. p. 125—126° (Found: C, 56·6; H, 5·2; S, 23·4. $C_{20}H_{22}O_4S_3$ requires C, 56·9; H, 5·2; S, 22·8%). It gave negative tests for thiol groups and was unaffected when heated under reflux in aqueous alcohol with sulphuric acid, but was converted by hot dilute sodium hydroxide into a viscous, semi-solid material.

3-*Iodo*-1-p-*tolylsulphonylprop*-1-*ene* (as XXI) was formed in good yield by heating the chloride (VI) and excess of sodium iodide in acetone under reflux for 3 hours. Recrystallisation from aqueous alcohol gave needles, m. p. 75° (Found: C, 37·15; H, 3·65; S, 10·5. $C_{10}H_{11}O_2SI$ requires C, 37·3; H, 3·45; S, 9·95%). In working up one preparation, the aqueous acetone mixture, after a week, deposited crystals of the alcohol (V) in over 10% yield, and this mobility of the iodine atom is confirmed by the rapid production of potassium iodide on treatment with hot dilute alcoholic potash. (XXI) was reduced in dilute acetic acid solution at 100°, by adding twice its weight of zinc dust during 2 hours, to *p*-tolyl allyl sulphone (Found: C, 60·9; H, 6·35. Calc. for $C_{10}H_{12}O_2S$: C, 61·2; H, 6·1%), m. p. 52°, undepressed on admixture with authentic *p*-tolyl allyl sulphone, but depressed by tolyl propyl sulphone, both of which were made by condensing sodium toluene-*p*-sulphinate with the corresponding aliphatic bromide (Otto, *Annalen*, 1894, **283**, 184; *J. pr. Chem.*, 1890, **40**, 562).

Isomeric Change of (VI) *into* 1-*Chloro*-3-p-*tolylsulphonylprop*-1-*ene*.—1-*Chloro*-3-p-*tolylsulphonylprop*-1-*ene* (IV) was obtained when 3-chloro-1-*p*-tolylsulphonylprop-1-ene (VI) (2 g.) was dissolved in benzene (5 ml.) and stirred vigorously with a solution of potassium hydroxide (0·01 g.) in water (20 ml.) at 50° for 1 hour, followed by addition of ether (20 ml.) and stirring for an additional 2 hours at 30°. After the ether had been allowed to evaporate off at room temperature, the product was collected and recrystallised from light petroleum containing a few drops of benzene. 0·9 G. (45%) of needles, m. p. 73°, containing halogen, was obtained (Found: C, 51·9; H, 5·1; S, 14·3. $C_{10}H_{11}O_2SCl$ requires C, 52·05; H, 4·8; S, 13·9%). Mixtures of (IV) with the isomer (VI) or the chlorohydrin (XI) gave considerable depressions in m. p. An emulsion of (XV) decolorised cold aqueous potassium permanganate after a few seconds. (IV) was unchanged on treatment with a solution of sodium iodide in boiling acetone (3 hours), on treatment with hot hydrochloric, sulphuric, or acetic acid, on vigorous stirring of a benzene solution with cold saturated aqueous sodium hydroxide for 3 hours, on exposure of an aqueous alcoholic or benzene–light petroleum solution to direct sunlight for 48 and 100 hours, respectively, or on heating it under reflux for 5 hours in light petroleum containing a trace of iodine. Treatment of (IV) with dilute ethanolic sodium hydroxide at 30° for 3 hours yielded the chloro-ether (XVIII), m. p. 78—79°, identified by mixed m. p., together with a small amount of the dioxan (XIV).

The propene (IV) was also obtained when the isomer (VI) (1 g.) was dissolved in 50% aqueous pyridine (10 ml.) and warmed at 70° for 2 hours and the mixture cooled and neutralised (yield, 0·4 g.). A difficultly separable mixture of (IV) and (VI) was obtained when (VI) was heated at 100° for 3 hours in aqueous benzenesulphonic acid solution; (IV) was isolated by virtue of its lower solubility in aqueous alcohol.

Synthesis of 1-*Chloro*-3-p-*tolylsulphonylprop*-1-*ene*.—1 : 3-Dichloropropene was prepared according to the method of Hill and Fisher (*J. Amer. Chem. Soc.*, 1922, **44**, 2584), by dehydration of *s*-glycerol dichlorohydrin with phosphoryl chloride. Sodium toluene-*p*-sulphinate (8·9 g.) and 1 : 3-dichloropropene (5·5 g.) were dissolved in aqueous alcohol (30 ml.), and the mixture made slightly acid to litmus, warmed on the water-bath for 3 hours, and cooled; an oil separated which solidified on storage. The mixture remained slightly acid. Recrystallisation from alcohol containing a drop of hydrochloric acid gave needles (7·0 g.), m. p. 65—68° undepressed on admixture with (IV). The compound contained halogen and decolorised cold aqueous permanganate in a few seconds.

3-p-*Tolylsulphonylpropane*-1 : 2-*diol* (XX; R = *p*-C_6H_4Me).—(*a*) Sodium toluene-*p*-sulphinate (8·9 g.) and glycidol (3·7 g.) in water (50 ml.) were warmed on a water-bath, and the solution was kept neutralised by titration with 2N-sulphuric acid as the reaction proceeded (phenolphthalein as indicator). After 5 hours, the reaction appeared to be complete (acid added, 18 ml.; theory, 25 ml.) and the solution was evaporated *in vacuo* to a small volume and extracted with chloroform. The extract yielded a

viscous, water-soluble syrup which crystallised only when the hot benzene solution was treated with a considerable amount of anhydrous magnesium sulphate and filtered hot. Further purification gave the glycol as plates, m. p. 74—75° (Found: C, 52·5; H, 5·9. $C_{10}H_{14}O_4S$ requires C, 52·2; H, 6·1%).

(*b*) The chlorohydrin (XI; R = *p*-C_6H_4Me, X = Cl) was heated with water in a sealed tube at 110—120° for 24 hours, and the resultant aqueous layer decanted from a little black oil, filtered, and evaporated on a water-bath. The residue partly solidified, and on drying on a porous tile and recrystallising from benzene with magnesium sulphate, it formed needles, m. p. 74—75°; mixed m. p. with product in (*a*) 73—75°.

(*c*) 3-*p*-Tolylthiopropane-1 : 2-diol (X) (2 g.) and 30% hydrogen peroxide (3 ml.) were dissolved in acetic acid (12 ml.) and kept for 8 days at 36°. The acetic acid was distilled off *in vacuo*, and the residue set aside on a watch-glass in the air. After 2 weeks, it crystallised, and rubbing with ether gave a white powder. Crystallisation from benzene with magnesium sulphate gave the glycol (XX; R = *p*-C_6H_4Me), m. p. 74—75° (not depressed by admixture with the glycol prepared as above).

This glycol (XX) with benzoyl chloride at 100° for 20 hours gave the *dibenzoyl* derivative, small needles, m. p. 133°, from alcohol (Found: C, 65·45; H, 4·95. $C_{24}H_{22}O_6S$ requires C, 65·75; H, 5·0%).

Phenylsulphonylpropane Derivatives.

3-*Phenylsulphonylprop*-2-*en*-1-*ol* (XII; R = Ph) was obtained as white plates (13·3 g.) when sodium benzenesulphinate (16·4 g.) and epichlorohydrin (9·3 g.) were dissolved in water (60 ml.) and alcohol (15 ml.) and kept at 32° for 2 days; it crystallises in long needles from water; m. p. 139—140° (Found: C, 54·5; H, 4·7. $C_9H_{10}O_3S$ requires C, 54·5; H, 5·05%). The unpurified product is contaminated with an appreciable amount of the dioxan (below). The propenol (XII) is also obtained as silky needles (0·6 g.), m. p. 135—137° (crude), by the action of water (25 ml.) on 1 : 2-dibromo-3-phenylsulphonylpropane (2 g.) in a sealed tube at 110—120° for 23 hours. A mixture with the alcohol (XII; R = Ph) melted at 137—138°. When heated with excess of benzoyl chloride at 100° for 20 hours, followed by removal of the excess with dilute sodium hydroxide, (XII; R = Ph) gave the *benzoyl* derivative, which crystallised from alcohol and a little water in long needles, m. p. 86—86·5° (Found: C, 63·4; H, 4·55. $C_{16}H_{14}O_4S$ requires C, 63·6; H, 4·65%). [Otto (*loc. cit.*) found C, 63·2; H, 5·3, though the dibenzoate of his "glycol," $C_{23}H_{20}O_6S$, requires C, 65·1; H, 4·7%.]

2 : 5-*Bisphenylsulphonylmethyldioxan* (XIV; R = Ph) was precipitated rapidly on warming the alcohol (XII; R = Ph) with dilute alkali. It forms glistening plates, m. p. 244°, from alcohol (Found: C, 54·2; H, 4·7. $C_{18}H_{20}O_6S_2$ requires C, 54·5; H, 5·05%).

3-*Chloro*-1-*phenylsulphonylprop*-1-*ene* was prepared from the alcohol (XII; R = Ph) and phosphorus pentachloride in the same way as for the tolyl homologue. From aqueous alcohol, it forms needles, m. p. 58·5° (Found: C, 49·8; H, 4·2; Cl, 16·3. $C_9H_9O_2SCl$ requires C, 49·9; H, 4·15; Cl, 16·4%). The 3-*bromo*-analogue, prepared from (XII; R = Ph) and phosphorus pentabromide, crystallises from ether–light petroleum in long, massive needles, m. p. 34—35° (Found: C, 41·3; H, 3·6. $C_9H_9O_2SBr$ requires C, 41·4; H, 3·45%).

3-*Iodo*-1-*phenylsulphonylprop*-1-*ene*.—The chloro-compound (2·5 g.) and sodium iodide (2·5 g.) were heated under reflux for 3 hours in acetone (30 ml.), and then water (200 ml.) was added. The *iodide* solidified and recrystallised from aqueous alcohol to form irregular, feathery crystals, m. p. 67—68° (Found: C, 35·2; H, 2·75. $C_9H_9O_2SI$ requires C, 35·1; H, 2·9%).

1-*Chloro*-3-*phenylsulphonyl*-2-*ethoxypropane* (XVIII; R = Ph, R′ = Et, X = Cl) resulted from warming 3-chloro-1-phenylsulphonylprop-1-ene with weak alcoholic alkali at 60° for 15 minutes. It crystallises from aqueous alcohol in prisms, m. p. 79° (Found; C, 51·1; H, 6·0; Cl, 13·9; S, 12·7. $C_{11}H_{15}O_3SCl$ requires C, 50·3; H, 5·7; Cl, 13·5; S, 12·2%).

Benzylsulphonylpropane Derivatives.

3-*Benzylsulphonylprop*-2-*ene*-1-*ol* (XII; R = CH_2Ph), from 1 : 2-dibromo-3-benzylsulphonylpropane (1·95 g.) and water (20 ml.) in a sealed tube at 120° for 3½ hours, was collected after cooling and crystallised from benzene in fine needles, m. p. 113—114° (Found: C, 56·6; H, 5·8. $C_{10}H_{12}O_3S$ requires C, 56·6; H, 5·65%). The m. p. 110—111° was given to the so-called 1-benzylsulphonylpropane-2 : 3-diol by van Zuydewijn (*loc. cit.*, p. 454), who prepared it in the above way and also by the action of peracetic acid and then water on benzyl allyl sulphone. It has now also been obtained (1·9 g.) from epichlorohydrin (1·2 g.) and sodium benzylsulphinate (2·2 g.) in aqueous alcoholic solution at 35° for 24 hours. It formed 2 : 5-*bisbenzylsulphonylmethyldioxan* (XIV; R = CH_2Ph) when heated in dilute aqueous alkali for several minutes. Insoluble in alcohol, benzene, and acetone, it dissolved readily in dioxan and crystallised from this solvent in short needles, m. p. 248—249° (sinters from 245°) (Found: C, 56·6; H, 5·5. $C_{20}H_{24}O_6S_2$ requires C, 56·6; H, 5·65%).

3-Chloro- and 3-bromo-1-benzylsulphonylprop-1-ene were obtained by the action of the appropriate phosphorus pentahalide on the alcohol (XII; R = CH_2Ph). The former gave needles, m. p. 70—71°, from benzene–light petroleum, and the latter crystallised from the same solvent in long, silky needles, m. p. 95—97°. They did not depress the m. p.s of authentic samples of the halides prepared by heating the corresponding dibromides with pyridine in benzene (Rothstein, *loc. cit.*).

3-Bromo-1-benzylsulphonylprop-1-ene (0·5 g.), isomerised by dilute alkali in the same way as the tolyl analogue, gave a product (0·1 g.) which crystallised from benzene–light petroleum as plates, m. p. 150—151°. Rothstein (*loc. cit.*, p. 312) records the melting point of 1-bromo-3-benzylsulphonylprop-1-ene as 151—152°. The mother-liquors in this case yielded a second *product* (0·3 g.), plates from benzene–light petroleum, m. p. 69°, which is also isomeric with these halides (Found: C, 43·9; H, 4·8. $C_{10}H_{11}O_2SBr$ requires C, 43·6; H, 4·0%).

Benzene solutions of these two compounds, m. p. 69° and 152°, were exposed in silica tubes to sunlight for 100 hours without appreciable change. The possibility of stereoisomerism is being further investigated.

3-Bromo-1-benzylsulphonylprop-1-ene, reduced with zinc and acetic acid in the manner described

for 3-iodo-1-*p*-tolylsulphonylprop-1-ene yielded benzyl allyl sulphone, identical with a specimen made after Rothstein (*J.*, 1934, 684).

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472. *Chemistry of the Interhalogen Compounds. Part II. Potassium Iodohexafluoride.*

By H. J. EMELÉUS and A. G. SHARPE.

Potassium fluoride combines with iodine pentafluoride to yield *potassium iodohexafluoride* (*hexafluoroiodate*), KIF_6. The structure of the $(IF_6)^-$ ion is discussed. The validity of Beck's claims (*Z. anorg. Chem.*, 1937, **235**, 77) to have prepared the compounds K_2ClF_7, K_2NOF_3, and $K_2N_2O_5F_2$ is questioned.

INDICATIONS of complex fluoride formation between potassium fluoride and iodine pentafluoride, analogous to that between potassium fluoride and bromine trifluoride, were mentioned in Part I (*J.*, 1948, 2135). Iodine pentafluoride is a much less vigorous fluorinating agent than bromine trifluoride, and at temperatures below its boiling point (97°) is without action on most metallic halides. It does, however, dissolve potassium fluoride, and removal of excess of the halogen fluoride by evaporation under 2—5 mm. pressure gives *potassium iodohexafluoride* (*hexafluoroiodate*), KIF_6.

Attention has so far been confined to the preparation of this salt, which is a white crystalline solid, sparingly soluble in cold, rather more soluble in hot, iodine pentafluoride. Water decomposes it, with evolution of heat, according to the equation

$$IF_6^- + 3H_2O = 6F^- + IO_3^- + 6H^+$$

Potassium iodohexafluoride is decomposed by heat, and the decomposition is rapid after it melts at *ca.* 200°; the residue is potassium fluoride. This general mode of decomposition of polyhalides, the most electronegative halogen remaining with the metal, is to be expected, since lattice energies in the alkali-metal halides decrease from fluoride to iodide, and formation of the fluoride (or, when fluorine is absent, the chloride) corresponds to the maximum decrease in energy. Carbon tetrachloride has no action on potassium iodohexafluoride, but dioxan produces slight decomposition. At low pressures (less than 1 mm.) the compound slowly loses iodine pentafluoride.

Potassium iodohexafluoride is the first reported well-defined polyhalide containing seven halogen atoms. Confirmation of its structure by *X*-ray analysis has not yet been possible, but its properties leave little room for doubt that it is to be formulated as $K^+(IF_6)^-$. Possible electronic and stereochemical configurations for such a complex fluoride ion are discussed below.

A claim to have prepared a compound formally similar to potassium iodohexafluoride has, however, been made by Beck (*loc. cit.*). The action of concentrated hydrofluoric acid on potassium chlorate was reported to yield the compound, K_2ClF_7 or $KF,KClF_6$; analytical data, but no other evidence, were quoted supporting this claim. By comparison with the new polyhalides described in Part I and here, it would be expected that a derivative of the as yet unknown chlorine pentafluoride would be a very unstable substance and would certainly be hydrolysed by 40% hydrofluoric acid. All attempts to repeat Beck's preparation have failed to yield anything but chlorate–fluoride mixtures, and it is believed that his claim is mistaken. In reaching this conclusion, account has been taken of other work described in the same paper, namely, the preparation of fluoronitrites, K_2NOF_3 and Na_2NF_6, and of the fluoronitrate $K_2N_2O_5F_2$, by the action of hydrofluoric acid on potassium nitrite, sodium nitrite, and potassium nitrate, respectively; and evidence for the production of a fluorocarbonate by the action of hydrofluoric acid on potassium carbonate. Beck's compound Na_2NF_6 has been shown by Zintl and Haucke (*Z. anorg. Chem.*, 1938, **237**, 45) to be sodium hydrogen fluoride; his K_2NOF_3 and $K_2N_2O_5F_2$ were found to be potassium acid fluorides, and a mixture of potassium acid fluoride and unchanged potassium nitrate, respectively; his evidence for fluorocarbonate formation is confined to a mistaken idea of the nature of calcium fluoride when precipitated in the cold. The

subject is discussed in more detail below : it may be taken that solid polyhalides in which chlorine forms the central atom of a complex anion have not yet been prepared.

The iodine atom in $(IF_6)^-$ should have a valency shell of fourteen electrons but only six-fold co-ordination; it thus differs from that in IF_7, and resembles rather the selenium and tellurium atoms in the ions $(SeCl_6)^{--}$, $(SeBr_6)^{--}$, and $(TeCl_6)^{--}$. In these (Engel, *Z. Krist.*, 1935, **90**, 341; Hoard and Dickinson, *ibid.*, 1933, **84**, 436) the configuration is octahedral, but, on the assumption that chlorine and bromine have their normal covalent radii, the octahedral radii of selenium and tellurium are unexpectedly large by 0·25 A., and it has been suggested by Beach (quoted by Pauling, " The Nature of the Chemical Bond," 1940) that the orbitals involved in bonding are, in the case of selenium, $4p^34d^25s$ hybridised orbitals and that the inert 4*s* orbital constitutes a separate energy level and is responsible for the long bond.

The necessity for d^2sp^3 bonding emerges from Kimball's systematic calculations of bond type and configuration (*J. Chem. Physics*, 1940, **8**, 194); no other combination of orbitals gives an octahedral structure. In the electrically neutral hexafluorides of selenium and tellurium, which have two valency electrons less than the complex halides, octahedral shape and almost normal bond length are satisfactorily reconciled with the obvious electronic configurations for the central atom : $4s^24p^64d^4$ for selenium, $5s^25p^65d^4$ for tellurium. For the iodine atom in $(IF_6)^-$ the expected electronic configuration is $5s^25p^65d^46s^2$ (unless the ion differs from all other known finite complex six-co-ordination ions by not being octahedral), and it may therefore be predicted that, unlike other polyhalide anions, in which the bond distances are the sums of the appropriate covalent radii (Wyckoff, *J. Amer. Chem. Soc.*, 1920, **42**, 1100; Pauling, *ibid.*, 1925, **47**, 1561; Mooney, *Z. Krist.*, 1938, **98**, 324, 377), the $(IF_6)^-$ ion will have an abnormally large interhalogen distance. The structure of the covalent IF_7 molecule (b. p. +4°) must be considered on its own merits; here the outermost fourteen electrons round the iodine nucleus presumably form seven bonds, probably $5s5p^35d^3$ bonds arranged in a distorted octahedron, a structure already known in the ion $(ZrF_7)^{---}$ (Hampson and Pauling, *J. Amer. Chem. Soc.*, 1938, **60**, 2702). There seems no reason to suggest an abnormal bond length in iodine heptafluoride.

If technical difficulties due to reactivity and difference in scattering power between the halogens can be overcome, structure determinations on these interhalogen ions and molecules should therefore provide useful experimental information about the relation between electronic configuration and stereochemical type.

Experimental.

Potassium Iodohexafluoride.—Quantities of up to 30 g. of iodine pentafluoride were conveniently prepared by passing fluorine over iodine in a quartz trap cooled by partial immersion in water and continuously shaken to prevent the formation of an inactive surface layer of the pentafluoride. The product was analysed by decomposition with sodium hydroxide, followed by determination of (i) iodine, by reduction with sulphurous acid and precipitation as silver iodide in the presence of dilute nitric acid, (ii) fluorine, by precipitation as calcium fluoride, (iii) oxidising power, by iodometric determination of the iodate formed (Found : I, 57·0; F, 42·2%; iodine liberation, 5·96 equivs. per mole. Calc. for IF_5 : I, 57·2; F, 42·8%; iodine liberation, 6·00 equivs. per mole).

Boiling iodine pentafluoride did not react with sodium, potassium, or silver chloride. Argentous and barium fluorides were almost insoluble in the reagent, but potassium fluoride dissolved (about 1 g. per 100 g. at the b. p.) and white crystals were formed on cooling this solution. Attempts to remove the solvent at low pressures (<1 mm.) in a simple vacuum system gave products of varying composition ($KF,0·6IF_5$ to $KF,0·9IF_5$), which continued to lose iodine pentafluoride slowly. Iodine pentafluoride forms a compound with dioxan (Scott and Bunnett, *J. Amer. Chem. Soc.*, 1942, **64**, 2727), and the possibility of removing the uncombined halogen fluoride with dioxan was studied, without, however, obtaining even a moderately pure product. This was finally obtained by removal of the iodine pentafluoride at 15—20° under a pressure of 2—5 mm. of mercury; under these conditions, the vapour pressure of the solvent is sufficient for its removal before dissociation of the deposited solute is appreciable. The whole preparation was conducted in quartz apparatus, and a constant weight was attained. Analysis by determination of potassium as sulphate, and of iodine, fluorine, and equivalent weight as an oxidising agent by the method used for iodine pentafluoride, established the identity of the product as moderately pure *potassium iodohexafluoride* (Found : K, 14·7; I, 43·6; F, 40·1%; equiv., 48·4. KIF_6 requires K, 13·9; I, 45·4; F, 40·7%; equiv., 46·7). Discrepancy with calculated results corresponds to the presence of 4% (molar) of potassium fluoride, arising from the method of preparation. Properties of potassium iodohexafluoride have been described above.

Reactions of 40% *Hydrofluoric Acid with Some Oxy-salts.*—Several attempts to prepare K_2ClF_7 by three times evaporating potassium chlorate with the acid (Beck, *loc. cit.*) yielded products containing K, 31—33; Cl, 14—23; F, 6—21% (Calc. for K_2ClF_7 : K, 31·7; Cl, 14·4; F, 53·8%). Water had no action on these products except to dissolve them without evolution of heat. Rapid recrystallisation of potassium chlorate from the boiling acid resulted in its recovery almost unchanged (Found : Cl, 25·4; F, 3·0. Calc. for $KClO_3$: Cl, 28·9%); repeated evaporation with the acid produced complete decomposition to fluoride, all the chlorine being removed. There is thus no evidence for an intermediate compound, and the reaction is gradual replacement of chlorate by fluoride.

Potassium bromate was completely and rapidly decomposed to the fluoride by warm hydrofluoric acid;

the iodate gave potassium difluoroiodate, KIO_2F_2 (Helmholtz and Rogers, *J. Amer. Chem. Soc.*, 1940, **62**, 1537).

The conditions described by Beck for the production of Na_2NF_4 and K_2NOF_3 (evaporation of nitrites with hydrofluoric acid) brought about elimination of all the nitrogen; the reactions which he quoted for the $(NOF_3)^{--}$ ion, erroneously stated to be iso-electronic with the sulphate ion, are in fact characteristic of fluorides. When potassium nitrate is heated with hydrofluoric acid, fluoride is substituted for nitrate and not for oxygen. Beck found that after three evaporations with hydrofluoric acid, the product contained: K, 35·8; F, 15·1%; no nitrogen determination was made on this or on his other products (Calc. for $K_2N_2O_5F_2$: K, 34·8; F, 16·0; N, 12·0%). We found on repetition of Beck's preparation: K, 38·8; F, 17·2; N, 9·4%. This indicates partial replacement of the nitrate. Beck actually observed that on further treatment the fluorine content of the product increased, but he attributed this to formation of fluorinated nitrates intermediate between potassium nitrate and (the highly unlikely) KNF_4.

Potassium carbonate and hydrofluoric acid were admitted to produce a vigorous evolution of carbon dioxide, but it was said (*loc. cit.*) that alcohol precipitated a substance which, dissolved in ice-cold water, gave only an opalescence with calcium chloride solution, warming being necessary for production of a precipitate. The character of the calcium fluoride precipitate is, however, well known, and since normal and acid potassium fluorides are all insoluble in alcohol, the evidence for the existence of a fluorocarbonate may be dismissed without further comment.

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473. *Oxidation of Aldehydes in the Gaseous Phase. Part I. Low-temperature Oxidation of Acetaldehyde.*

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The oxidation of acetaldehyde in the gas phase has been investigated at 120° and it is shown that it is a radical chain reaction, the rate of which is governed by the equation $-d[CH_3{\cdot}CHO]/dt = k[CH_3{\cdot}CHO]^2$. Nitrogen peroxide and *iso*propyl alcohol inhibit the oxidation but nitrogen has no effect on it. Increasing the surface-volume ratio by a factor of ten increases the rate of the reaction by about 60%. A reaction mechanism is proposed which accounts for the experimental observations.

THE thermal oxidation of acetaldehyde in the gaseous phase was first investigated in detail by Bodenstein and his students (*Sitzber. preuss. Akad.*, Phys.-Math. Kl., 1931, III, 1; *Z. physikal. Chem.*, 1931, **12**, *B*, 151), who studied the reaction between 55° and 90°. At these temperatures there is a decrease in pressure as the reaction proceeds, and the main product is not acetic acid but peracetic acid. Bodenstein states that the reaction is characterised by long and irregular induction periods and that its rate is proportional to the square of the acetaldehyde concentration and inversely proportional to the oxygen concentration. In the light of these results Bodenstein put forward a mechanism which yielded an equation for the overall reaction in agreement with his experimental data. There were, however, many unsatisfactory features in this work, and the reaction was later investigated in greater detail by Hatcher, Steacie, and Howland (*Canadian J. Res.*, 1932, **7**, 149), who studied the reaction between 60° and 120° and carried out a fairly complete analysis of both liquid and gaseous products, and brought to light many interesting features. Their results agreed with Bodenstein's in showing that the rate of the reaction was approximately proportional to the square of the acetaldehyde concentration, but they found that it was uninfluenced by the oxygen concentration. They observed a slight induction period at the commencement of the reaction but it was very much smaller than those observed by Bodenstein, and for this reason they suggested that the irregular induction periods which he observed must have been due to impurities. Hatcher, Steacie, and Howland further differed from Bodenstein in stating that they found one of the reaction products to be formic acid. Though they were somewhat critical of Bodenstein's researches they agreed that the apparent activation energy for the reaction is about 10 kcals. and that the reaction is influenced by the surface of the reaction vessel.

This work of Hatcher, Steacie, and Howland is open to criticism on two points. First, they pre-mixed the acetaldehyde and the oxygen in the presence of mercury, a procedure which is objectionable for it is known that mercury catalyses the reaction between aldehydes and oxygen (Hatcher, Steacie, and Rosenberg, *J. Physical Chem.*, 1934, **38**, 1189); secondly, they used a mercury manometer to follow the course of the reaction. It has been shown on a number of occasions that one obtains erroneous results if a mercury manometer is used in the study of the oxidation of aldehydes (Snowden and Style, *Trans. Faraday Soc.*, 1939, **35**, 426; Newett, Baxt, and Kelkar, *J.*, 1939, 1703). This objection also applies to the work of Pease (*J. Amer. Chem. Soc.*, 1933, **55**, 2753) who later investigated the reaction at 120°. Pease did not pre-mix his

gases and his results agree reasonably well with those of Hatcher, Steacie, and Howland, though he differed from them in one important aspect, namely, he did not find any carbon dioxide in his gaseous reaction products except when the reaction vessels were coated with potassium chloride. He found that the rate of the reaction was proportional to the square of the acetaldehyde concentration and uninfluenced by the oxygen concentration. He further showed that the oxidation is inhibited by ethyl alcohol vapour but uninfluenced by water vapour and nitrogen, and concluded that it was probably a chain reaction. Pease carried out a few experiments to investigate the effect of the surface-volume ratio on the rate of reaction and also studied the effect of coating the surface of the reaction vessel with potassium chloride. From these experiments he concluded that the chains probably started on the walls of the vessel and ended in the gas phase. Because of the differences in the experimental results of these various workers, we have re-examined this reaction. Further, a knowledge of the mechanism of the oxidation of acetaldehyde is important in the study of the oxidation of organic compounds in general and it seemed desirable to attempt to discover the mechanism by which this reaction occurred.

In this investigation we have avoided the use of mercury manometers for pressure measurements and have taken considerable care to purify our acetaldehyde and oxygen. We have also analysed the liquid reaction products immediately after an experiment for it has been shown that erroneous results are obtained unless the mixture of acids and unchanged aldehyde is analysed without delay.

Experimental.

Apparatus.—The general apparatus assembly was of the conventional high-vacuum type, the reaction vessel being made from Pyrex tubing of 40 mm. diameter. The volume was determined experimentally as 214·6 c.c. The temperature of the electric furnace could be controlled to $\pm 0{\cdot}2°$ by means of a " Sunvic " energy regulator. The rate of the reaction was followed by observing the pressure change by either a glass " Bourdon " type manometer or a metal bellows manometer of the type described by East and Kuhn (*J. Sci. Instr.*, 1946, **23**, 185). Both these manometers were used as null instruments and it was found that reproducible results were obtained when the gauges were interchanged.

As the reaction was very sensitive to surface impurities, great care had to be taken in cleansing the vessel. This was usually done by filling it with chromic acid and setting it aside, and then rinsing it with water for several hours. It was then sealed in position, and evacuated and baked in the furnace for several hours. Several trial runs had to be made until reproducible results were obtained.

Materials.—The acetaldehyde was purified by distilling the "pure" commercial product in an atmosphere of nitrogen, and dried by passing the vapour over calcium chloride. It was then redistilled several times in a vacuum, being condensed each time at $-80°$ in a " cardice "–acetone cooled trap. It was stored in a darkened vessel closed by a metal needle-valve, as it had been found that traces of tap grease appeared to accelerate the polymerisation of the acetaldehyde.

The oxygen was prepared by electrolysis of sodium hydroxide and freed from hydrogen by passing it over heated platinised asbestos, and from carbon dioxide by " Carbosorb." It was dried by passing it over phosphoric oxide.

The *iso*propyl alcohol was purified and freed from acetone by heating it under reflux for 3 or 4 hours with 2 : 4-dinitrophenylhydrazine, and then fractionating it in a stream of nitrogen. It was then distilled under vacuum and stored under its own vapour.

Nitrogen peroxide was prepared by heating lead nitrate in a stream of oxygen. The product was passed over phosphoric oxide and condensed in a trap at $-80°$. It was purified by several distillations under vacuum and stored in solid form at $-80°$ until required.

Analysis of Products.—The reaction products were removed from the vessel by means of a Töpler pump through a trap at $-80°$. The non-condensable gases were collected over mercury, and their volume determined. Aliquot portions were then analysed for residual aldehyde, residual oxygen, carbon monoxide, carbon dioxide, and hydrocarbons by means of a modified Bone–Newitt gas-analysis apparatus. The condensable material in the $-80°$ trap was dissolved in water and analysed as follows. A portion was titrated with N/100-potassium hydroxide using phenolphthalein as indicator; this gave the total carboxylic acids. A second portion was analysed for peroxide by adding a known volume of standard hydrochloric acid and excess of potassium iodide, the liberated iodine being titrated with N/100-sodium thiosulphate solution. Phenolphthalein was then added, and the residual acid determined by titration with N/100-potassium hydroxide. Only acyl peroxides and hydrogen peroxide react immediately with acidified potassium iodide to liberate iodine, so the above method yields the amount of peracetic acid or hydrogen peroxide in our condensable reaction products. Peracetic acid and hydrogen peroxide react with the above reagents as follows :

$$CH_3{\cdot}CO_3H + HCl + 2KI = CH_3{\cdot}CO_2K + KCl + H_2O + I_2$$
$$H_2O_2 + 2HCl + 2KI = 2KCl + 2H_2O + I_2$$

Since in both cases 2 equivs. of acid are necessary to produce 2 equivs. of iodine it is impossible by this method to determine the two peroxides separately, but the fact that the total peroxides given by this method sometimes exceeded the total carboxylic acids in the condensable reaction products must mean that some hydrogen peroxide was also produced as this is the only *neutral* peroxide which reacts with acidified potassium peroxide as rapidly as peracetic acid. A third portion was analysed for unchanged acetaldehyde by adding excess of hydroxylamine hydrochloride and titrating the liberated acid with N/100-potassium hydroxide using bromophenol-blue as indicator.

Experimental Results.

A typical pressure–time curve for the reaction at 120° is shown in Fig. 1: after a brief induction period, the pressure decreases steadily and at a uniform rate over the major part of the reaction. Towards the end of the reaction there is a decrease in the rate of pressure charge and finally the pressure increases slightly. By choosing the acetaldehyde and oxygen concentrations to correspond with one of Pease's (*loc. cit.*) experiments we found that our pressure–time curve agreed with his results for a vessel of similar dimensions. Pease observed this increase of pressure towards the end of the reaction but did not investigate it. We have carried out some runs at higher temperatures and found that this increase in pressure after the minimum pressure was more pronounced and must be attributed to the thermal decomposition of either peracetic acid or the peracetyl radical (see following paper).

FIG. 1.

Typical reaction curve.

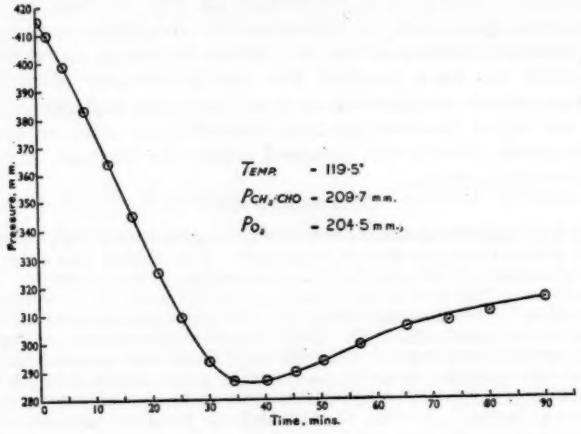
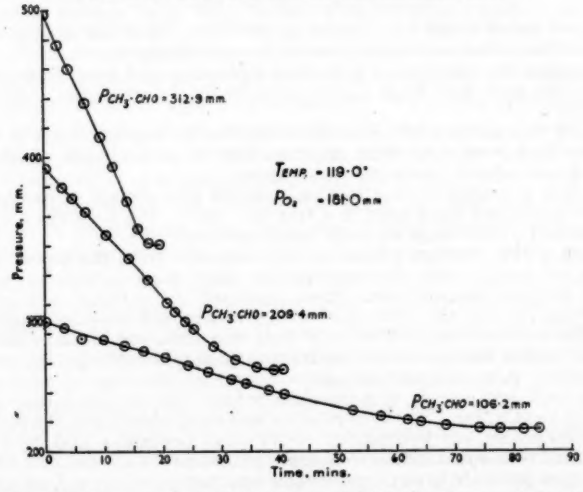


FIG. 2.

Effect of variation in aldehyde concentration.



Throughout this investigation we found that the slight induction period at the commencement of the reaction was reproducible. In general, the reaction was stopped at the point where no further decrease in pressure occurred, and the mixture was pumped off and analysed. For a few mixtures, however, we made analyses at different intervals throughout the whole reaction in order to see how the yield of products varied during the course of the reaction.

Effect of Aldehyde Concentration.—The effect of acetaldehyde concentration on the rate of reaction was investigated by varying the acetaldehyde concentration while keeping that of the oxygen constant. The pressure–time curves for three runs are shown in Fig. 2, and in the following table we give the time (t_{10-60}) required for the pressure to drop from 10 to 60 mm. below the original value. It will be observed that an increase in the acetaldehyde concentration produces a marked increase in the rate of the reaction. By plotting the logarithm of $1/t_{10-60}$ against the logarithm of the aldehyde concentration a straight line

was obtained. From the slope of this graph we find that the rate varies as $A^{1.87}$ at 120°. This is in good agreement with the value obtained by Hatcher, Steacie, and Howland (*loc. cit.*) though slightly lower than the value of 2 obtained by Pease.

Variation of rate of reaction with acetaldehyde concentration.

Aldehyde, mm. Hg	312·9	209·4	106·2
O_2, mm. Hg	182·8	180·7	180·0
t_{10-60}, mins.	5·6	11·6	42·6

FIG. 3.

Effect of variation in oxygen concentration.

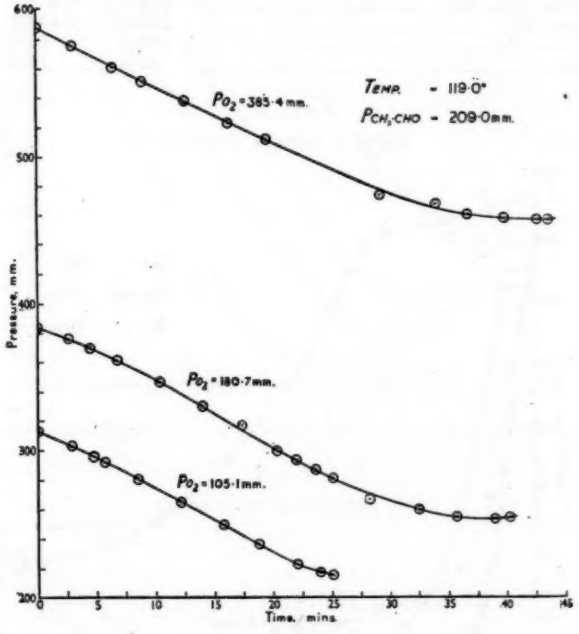
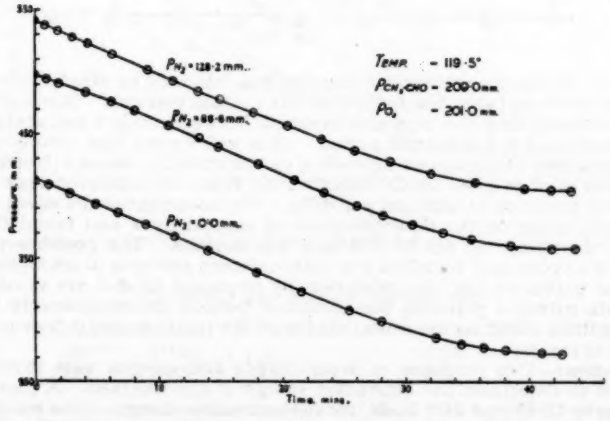


FIG. 4.

Effect of nitrogen.



Effect of Oxygen Concentration.—In a similar manner by varying the oxygen concentration while keeping the acetaldehyde concentration constant it was found that oxygen had little effect on the reaction rate over a wide range of concentration change. The pressure–time curves are shown in Fig. 3, and below we give the values of t_{10-60} for the various oxygen concentrations.

Effect of oxygen concentration on rate of reaction.

Oxygen, mm. Hg	385·4	180·7	105·1
Acetaldehyde, mm. Hg	202·7	209·4	209·4
t_{10-60}, mins.	12·6	11·6	11·8

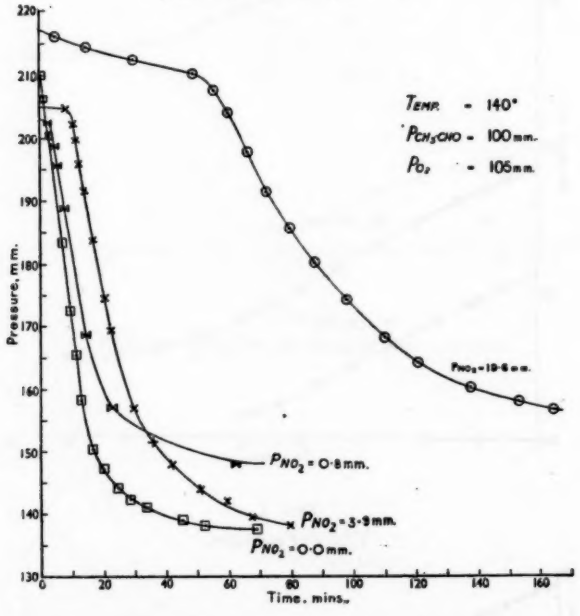
These results are in agreement with the negligible effect of oxygen concentration on the maximum rate of reaction as found by Hatcher, Steacie, and Howland (*loc. cit.*) and by Pease (*loc. cit.*), but in disagreement with Bodenstein's work which showed that the reaction was inhibited by oxygen.

Effect of Inert Gases.—The effect of inert gas was investigated by adding varying amounts of nitrogen to a given acetaldehyde–oxygen mixture. The following table gives the results of the experiments, and the pressure–time curves are shown in Fig. 4. These show clearly that the rate of the reaction is uninfluenced by inert gases.

Acetaldehyde, mm. Hg	209·5	208·9	209·5
Oxygen, mm. Hg	200·9	199·7	201·9
Nitrogen, mm. Hg	128·2	86·6	0
t_{10-60}, mins.	12·2	12·6	11·8

FIG. 5.

Effect of nitrogen peroxide.



Effect of Inhibitors.—Pease found that the reaction was inhibited by ethyl alcohol vapour but not by water vapour and so concluded that the oxidation was a chain reaction. Kane (*Proc. Roy. Soc.*, 1939, **171**, *A*, 251), while investigating the explosive reaction between oxygen and acetaldehyde, found that nitrogen peroxide lengthened the induction period. It is well known that nitrogen peroxide can act as an inhibitor or as a sensitiser of explosions depending on the quantity present (Norrish and Griffith, *ibid.*, 1933, **139**, *A*, 147), but even at quite small concentration Kane still observed that the induction period was lengthened by the presence of nitrogen peroxide. We investigated the effect of nitrogen peroxide and *iso*propyl alcohol vapour on the slow oxidation of acetaldehyde and found that both inhibit the reaction. However, they seem to act by different mechanisms. The pressure–time curves at 140° for a given mixture of oxygen and acetaldehyde with different amounts of nitrogen peroxide are shown in Fig. 5, and similar curves at 120° for inhibition by *iso*propyl alcohol are shown in Fig. 6. It will be observed that with nitrogen peroxide the induction periods are considerably lengthened, whereas *iso*propyl alcohol has little effect on the initial stages of the reaction and it seems mainly to affect the general overall rate of reaction.

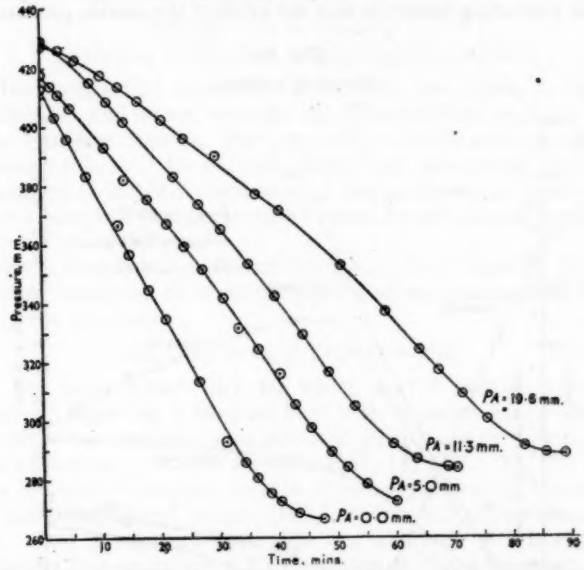
Effect of Temperature.—Two mixtures of acetaldehyde and oxygen were investigated at different temperatures in order to determine the activation energy of the reaction. A plot of the logarithm of $1/t_{10-60}$ against $1/T$ gave 13·96 and 14·6 kcals. for the activation energy of the reaction, both somewhat higher than the values of 10 kcals. given by Bodenstein and 8·7 kcals. given by Hatcher, Steacie, and Howland.

Effect of Surface/Volume Ratios.—The surface/volume ratio was increased ten-fold by packing the reaction vessel with lengths of 2-mm. Pyrex capillary tubing. A mixture containing 212·5 mm. of acetaldehyde and 200 mm. of oxygen was allowed to react at 120° and 131°. Reproducible results were

obtained after a few preliminary runs, and the vessel was then detached from the reaction system, the capillary tubes removed, the vessel replaced, and the rate of the reaction measured. A ten-fold increase

FIG. 6.

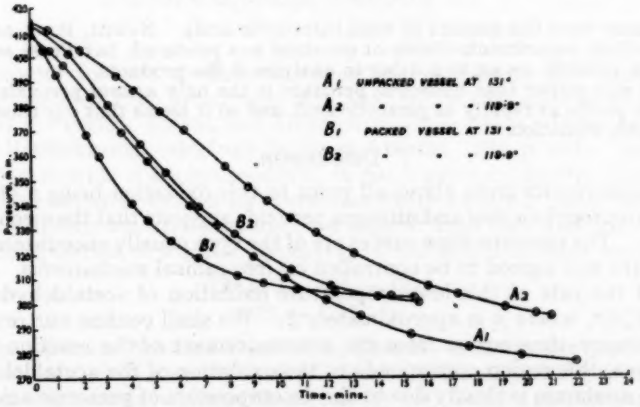
Effect of iso*propyl alcohol.*



Temp., 120°. $P_{O_2} = 200$ mm. (approx.). $P_{CH_3 \cdot CHO} = 210$ mm. P_A = pressure of *iso*propyl alcohol.

FIG. 7.

Effect of increasing surface.



in the surface/volume ratio only increased the rate of reaction by about 60%. The relevant figures are given in the following table.

Effect of varying surface/volume ratio.

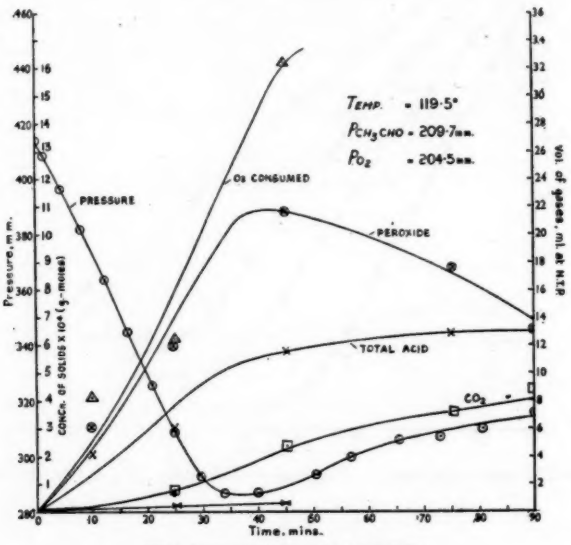
Surface/volume ratio.	Temp.	t_{10-60}.	Ratio.	Surface/volume ratio.	Temp.	t_{10-60}.	Ratio.
15·28	120°	4·14	1·5	15·28	131°	2·63	1·7
1·46	120	6·23		1·46	131	4·47	

Course of the Reaction.—A series of runs were done at 119·5° with a mixture of constant composition, *viz.*, 209·7 mm. of acetaldehyde and 204·5 mm. of oxygen. The reaction was stopped at intervals, and the products pumped off and analysed. The results are shown in Fig. 8 together with the pressure–time curve for this particular mixture. There are many interesting features in these results. First, we see clearly that the main condensable products of the oxidation are peroxides, and further that carbon monoxide and dioxide are produced throughout the reaction in agreement with the work of Bodenstein,

and of Hatcher, Steacie, and Howland but contrary to the findings of Pease. It will also be noted that the maximum yield of peroxides corresponds with the minimum in the pressure–time curve and that as the pressure starts to increase the yield of peroxide decreases, but the amount of carbon dioxide produced commences to increase. During this period there is practically no increase in the total amount of carboxylic acids; hence, we must conclude that the increase of pressure after the minimum is due to the decomposition of the peracetic acid or the peracetyl radical, this decomposition yielding an acid as one of its products. Another interesting feature is that the amount of peroxide produced throughout most of

FIG. 8.

Course of reaction.



(The lowest line refers to CO.)

the reaction is greater than the amount of total carboxylic acids. Newitt, Baxt, and Kelkar (*loc. cit.*) also noted that in their experiments excess of peroxide was produced, but Pease seems never to have observed an excess, possibly owing to a delay in analysis of the products.

It was pointed out earlier that hydrogen peroxide is the only *neutral* peroxide which reacts with acidified potassium iodide as rapidly as peracetic acid, and so it seems that our results must mean that it is produced in this oxidation.

DISCUSSION.

The experimental results given above all point to this oxidation being a chain reaction, and the inhibition by *iso*propyl alcohol and nitrogen peroxide suggests that the mechanism is probably a free-radical one. The pressure–time curves are of the type usually encountered in autoxidation processes, which are now agreed to be controlled by free-radical mechanisms. Our experiments show clearly that the rate of this low-temperature oxidation of acetaldehyde is given by the expression $R = k[A]^n$, where n is approximately 2. We shall confine our remarks here to the portion of the pressure–time curves from the commencement of the reaction to the minimum, for, as shown above, this region corresponds to the oxidation of the acetaldehyde. The rise in pressure after the minimum is clearly due to the decomposition of peracetic acid or the peracetyl radical and will be discussed later (see following paper).

Bodenstein originally put forward a thermal-chain mechanism to account for his experimental results. His mechanism was:

$$A = A^* \quad . \quad . \quad . \quad . \quad . \quad (1)$$
$$A^* + O_2 = P^* \quad . \quad . \quad . \quad . \quad (2)$$
$$P^* + A = P + A^* \quad . \quad . \quad (3)$$
$$P^* + O_2 = P + O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$
$$P^* + \text{wall} = P \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

This mechanism leads to the kinetic expression $d[P]/dt = k[A]^2/([O_2] + 150)$. Later, Bodenstein (*Z. physikal. Chem.*, 1931, **12**, *B*, 153) identified A with the acetyl radical and P with $CH_3{\cdot}CH\langle{}^{O}_{O}\rangle O$.

Though Bodenstein later (*Rec. Trav. chim.*, 1940, **59**, 48) modified his ideas slightly by adopting a general free-radical scheme, he again put forward essentially the same mechanism.

It should be noted that the photochemical oxidation of acetaldehyde has been shown to be a chain reaction (Bowen and Tietz, *J.*, 1930, 234; Carruthers and Norrish, *J.*, 1936, 1036).

A satisfactory mechanism for the photo-oxidation of acetaldehyde was first given by Bäckström (*Z. physikal. Chem.*, 1934, *B*, **25**, 115). In this mechanism it is assumed that the chains are propagated by the reactions:

$$CH_3{\cdot}CO + O_2 = CH_3{\cdot}CO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$CH_3{\cdot}CO_3 + CH_3{\cdot}CHO = CH_3{\cdot}CO_3H + CH_3{\cdot}CO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

This suggestion has been utilised by Ubbelohde (*Proc. Roy. Soc.*, 1935, *A*, **152**, 382) in his theory of hydrocarbon oxidation, and more recently by Hinshelwood and his co-workers (Labile Molecule Discussion, Faraday Society, 1947, p. 117). Lewis and von Elbe ("Combustion, Flames and Explosions of Gases," Cambridge, 1938) and Bodenstein (*Rec. Trav. chim.*, 1940, **59**, 48) have also adopted it in their discussion of the oxidation of acetaldehyde, the former observing that it is the simplest and most direct route by which one could conceive peracetic acid being formed from acetaldehyde.

We are of the opinion that the above reactions are, in fact, those by which peracetic acid is formed in the gas-phase oxidation of acetaldehyde; and we assume that the acetyl radical is produced initially by the reaction:

$$CH_3{\cdot}CHO + O_2 = CH_3{\cdot}CO + HO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Such a reaction is the most direct way by which acetyl radicals could be formed from acetaldehyde and, though there has in the past been little experimental evidence for the stability of the HO_2 radical, yet it has recently been detected during a mass-spectrometric study of the oxidation of propane (Eltenton, *J. Chem. Physics*, 1947, **15**, 478). By the inclusion of such an initiation process we are able to explain certain of our experimental observations. Whatever may be the fate of the perhydroxyl radical (HO_2), one would expect that hydrogen peroxide would be produced. This is in agreement with our analyses, which suggest that hydrogen peroxide is formed during this oxidation. Examination of Fig. 8, however, shows that the rate of production of peroxides is greater than the rate of production of acids, *i.e.*, it suggests that there must be some terminating reaction which is also giving hydrogen-peroxide or its precursor. Thus we are lead to postulate that the terminating process is *

$$CH_3{\cdot}CO_3 + O_2 = HO_2 + {\cdot}CH_2{\cdot}CO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$\downarrow$$

$$H_2CO + CO_2$$

This reaction accounts for the production of carbon dioxide in the oxidation, and also for formaldehyde, which has been found to be a product of the oxidation of all higher aldehydes (Ubbelohde, *loc. cit.*; Egerton, Smith, and Ubbelohde, *Phil. Trans.*, 1934, **A**, **234**, 484; Jost, "Explosions- und Verbrennungs-vorgänge in Gasen," Berlin, 1939, p. 534). In the oxidation of acetaldehyde, carbon dioxide is always produced in much greater quantity than the monoxide; this suggests that the latter is formed by a reaction aside from the main chain. Since small quantities of hydrocarbons are also produced, we suggest that they and the carbon monoxide arise from the decomposition of a small proportion of the acetyl radicals, *viz.*:

$$CH_3{\cdot}CO = CH_3 + CO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$2CH_3 = C_2H_6, \text{ etc.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Bawn and Tipper (Labile Molecule Discussion, Faraday Society, 1947, p. 103) have shown that methyl radicals can yield methane and ethylene besides dimerising to ethane.

This mechanism which we have just outlined, *viz.* (1)—(4), besides accounting for the products of the reaction, yields the correct form of the rate expression. By the usual method of stationary states we obtain:

$$-d[CH_3{\cdot}CHO]/dt = k_1[CH_3{\cdot}CHO][O_2] + k_1k_3[CH_3{\cdot}CHO]^2/k_4 \quad . \quad . \quad . \quad . \quad (7)$$

If we assume that the rate of initiation is much slower than the rate of propagation we get

$$-d[CH_3{\cdot}CHO]/dt \sim k_1k_3[CH_3{\cdot}CHO]^2/k_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

in agreement with our experimental results.

* The referees have pointed out that it would be better if the terminating reaction involved the destruction of the radical produced in the oxidation process. It is necessary, however, to have a terminating reaction such as the one given to obtain agreement with the experimental rate equation and to account for many of the experimental observations; and we have been unable to suggest any more reasonable reaction which is at the same time in keeping with the experimental facts.

The experimental activation energy for this reaction is, by equation (8), equal to $E_1 + E_3 - E_4$; E_3 and E_4 will be small and of the same order of magnitude though it is possible that E_4 might be slightly greater than E_3. In any event, however, practically the whole of the activation energy will be due to E_1. It is difficult to estimate E_1 with any high degree of accuracy, for there is some doubt as to the correct value for the dissociation energy of the aldehydic C–H bond, and also some uncertainty as to the correct heat of formation of the HO_2 radical. In the past, various values from 45 to 52 kcals. have been quoted for the heat of formation of HO_2; but these have been at the best inspired guesses, and there are no compelling reasons for accepting any of these values. Recently, it has been suggested (Walsh, *J.*, 1948, 331, that it might even be $\geqslant$60 kcals. Similar uncertainty prevails concerning the strength of the aldehydic C–H bond; in this case it has not always been realized that in chemical reactions one is interested in the dissociation energy of the bond and not its bond energy. Now from force-constant data (Linnett, *Trans. Faraday Soc.*, 1945, **41**, 223) it is demonstrable that the bond energy of the aldehydic C–H bond in acetaldehyde is less than the corresponding value for formaldehyde. Skinner (*ibid.*, p. 645) has shown how the bond energies of C–H bonds vary with the length of the linkage. The length of this bond in formaldehyde being taken as 1·11 A. (Dicke and Kistiakowsky, *Physical Rev.*, 1934, **45**, 4), Skinner's data yield a value of approximately 95 kcals. for the bond energy of this linkage (see also Long and Norrish, *Proc. Roy. Soc.*, 1948, **187**, *A*, 33). Since the force constant of the aldehydic C–H bond in acetaldehyde is smaller than that in formaldehyde, we can safely assume that the bond energy will be about 92—93 kcals. Now the dissociation energy of the C–H bond in formaldehyde will be less than the bond energy by an amount equal to the reorganisation energy of the formyl radical. The latter is at present an unknown quantity but it might be as high as 20 kcals. (Walsh, Labile Molecule Discussion, Faraday Society, 1947, p. 172), *i.e.*, the dissociation energy of CH in formaldehyde may be 75 kcals. This is in agreement with the value of 78 kcals. suggested by Gorin (*J. Chem. Physics*, 1939, **7**, 256) and the value of 73—83 kcals. recently given by Gerö and Valatin (*J. Chem. Physics*, 1948, **16**, 1014).

We can find some support for these estimates in the recently determined value of 21 kcals. for the activation energy of the thermal oxidation of formaldehyde (Axford and Norrish, *Proc. Roy. Soc.*, 1947, **192**, *A*, 518). By a similar argument to that given above, it can be shown that practically the whole of this activation energy is due to the initiation reaction, and we have recently shown (*Nature*, 1948, **162**, 367) that an initiation reaction analogous to reaction (1) leads to the same rate equation as that given by Axford and Norrish. Thus, taking the heat of formation of the HO_2 radical as ~52—62 kcals., we get a value of 72 ~ 83 kcals. for the dissociation energy of the C–H bond in formaldehyde.

The reorganisation energy of the acetyl radical may not be so great as that of the formyl radical, but its dissociation energy may be expected to be of the same order as the C–H bond in formaldehyde, since the bond energy of the aldehydic C–H in acetaldehyde is less than the corresponding datum for formaldehyde. Using the data given by Gerö and Valatin (*loc. cit.*), it is possible to calculate the energy for the process $CH_3{\cdot}CHO = CH_3 + H(^2S) + CO(X^1\Sigma)$ as ~99 kcals. Now, taking the activation energy for the reaction $CH_3{\cdot}CO = CH_3 + CO$ to be 18 kcals. (Herr and Noyes, *J. Amer. Chem. Soc.*, 1940, **62**, 2052), we calculate the dissociation energy of the aldehydic CH in acetaldehyde to be ~81 kcals. Since the heat of formation of the HO_2 radical is probably ~60 kcals., we get for E_1 the value ~21 kcals. The experimental activation energy is ~14 kcals.; there is thus a difference of ~7 kcals. to be accounted for. There are two obvious explanations. The initiation may be a surface reaction, in which case the activation energy would be lowered by the heat of adsorption of the reactants. The experimental data do show an increase in the rate when the surface volume ratio is increased, but it is difficult to say whether this justifies one in assuming that the surface plays a predominant part in the initiation process. In any case, the heat of adsorption would probably be greater than 7 kcals. On the other hand, it is highly probable that the difference between E_1 and $E_{obs.}$ is simply due to $E_3 - E_4$ being approximately equal to 7 kcals., in which case the thermochemistry of the proposed initiation process is satisfactory.

We should like to thank Messrs. G. Nodder and K. Paget for their skill in constructing the bellows manometer. One of us (J. H. T.) thanks the University of Liverpool for a Campbell Brown Fellowship.

THE UNIVERSITY, LIVERPOOL. [*Received, September 21st*, 1948.]

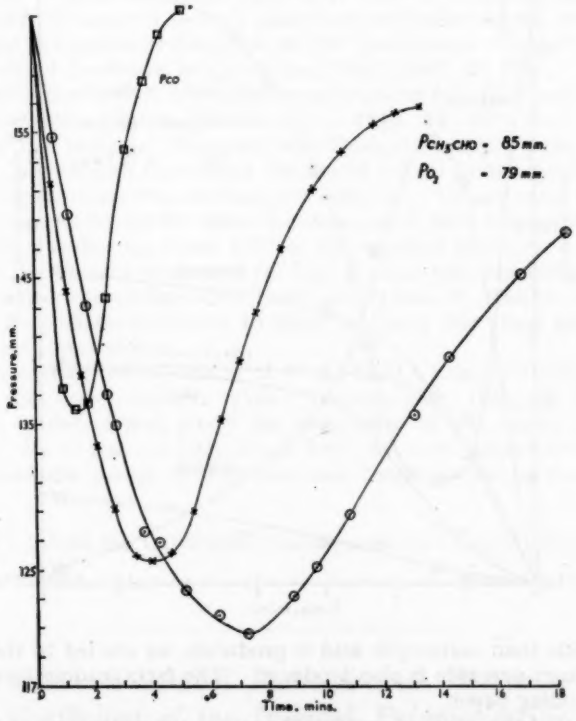
474. *Oxidation of Aldehydes in the Gaseous Phase. Part II. Oxidation of Acetaldehyde in the Pre-explosion Region: Thermal Stability of the Acetyl Radical.*

By C. A. McDowell and J. H. Thomas.

The oxidation of acetaldehyde has been studied in the pre-explosion region at temperatures from 170° to 200°. It has been found that there is an initial decrease in pressure which coincides with the formation of peracetic acid, and then an increase of pressure which is due to the decomposition of the per-acid. In view of the fact that the acetyl radical plays an important part in the oxidation of acetaldehyde (see preceding paper), these results can only be interpreted as showing that this radical is more stable than has hitherto been supposed.

In this paper we describe further experiments on the oxidation of acetaldehyde carried out at temperatures just below the cool-flame ignition temperatures for the mixtures studied. The method of investigation was the same as that described in the previous paper.

Fig. 1.



□ 196·5°. × 182·8°. ○ 175·8°.

The pressure–time curves for the reaction at 120° showed an upward trend after the minimum, which seemed to be due to peracetic acid or the peracetyl radical decomposing to yield carbon dioxide and a carboxylic acid. Experiments at higher temperatures with acetaldehyde and oxygen concentrations chosen so as to be just outside the explosion limits show that this upward trend after the minimum in the pressure–time curves is now greatly accentuated. Fig. 1 shows a series of curves for a given acetaldehyde–oxygen mixture at temperatures from 170° to 196·5°.

The course of the reaction has been investigated by allowing a chosen mixture to react for a certain time, and then pumping off the contents of the vessel and analysing the products. Analytical methods identical with those described in the preceding paper were employed, and the results for a particular mixture at 196·5° are shown in Fig. 2.

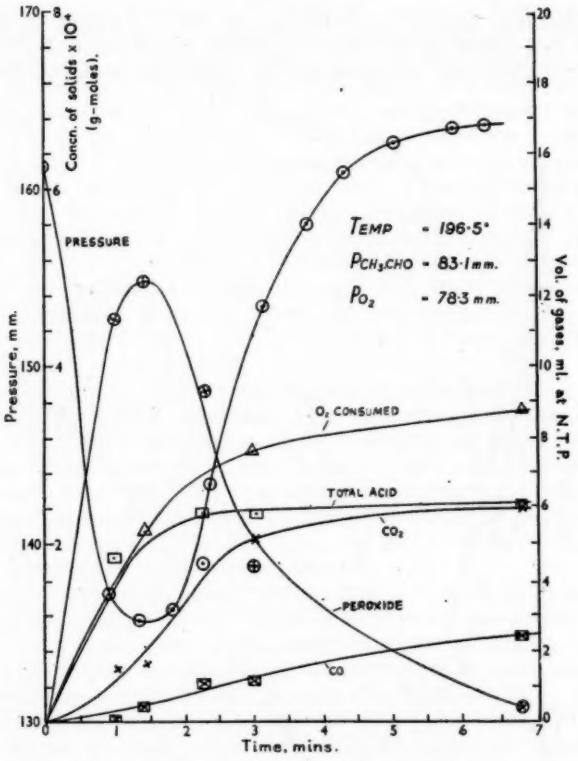
Examination of the curves in this figure shows beyond doubt that the upward trend in the

pressure is due to the decomposition of peracetic acid or the peracetyl radical into a carboxylic acid and carbon dioxide.

In connection with Fig. 2 it is again interesting to examine the curves showing the yield of peroxides and carboxylic acids. As in the previous paper, we see that the yield of peroxide increases as the pressure falls to a minimum and then the amount of peroxide begins to fall off; but the amount of carboxylic acid rises gradually and then remains stationary. Shortly after the minimum in the pressure–time curve, the yield of peroxide falls below that of the carboxylic acids, and by the time the pressure reaches its maximum and remains fairly stationary, the amount of peroxide in the system has fallen to practically zero. Since in the early stages of the

FIG. 2.

Course of the reaction.



reaction more peroxide than carboxylic acid is produced, we are led to the view that, besides peracetic acid, hydrogen peroxide is also produced. The facts leading to this view have been discussed in the preceding paper.

We have investigated the effect of varying the initial concentrations of the reactants in this high-temperature region and find that variation of the oxygen concentration has little effect on the rate either of decrease or of increase of pressure in the pressure–time curves. Variation of the acetaldehyde concentration affects both the rate of decrease and the rate of increase of pressure during the course of the reaction. This is only to be expected, for it was shown in the previous paper that the rate of formation of peracetic acid was proportional to the square of the acetaldehyde concentration. Similarly, for a fixed amount of oxygen, increasing the acetaldehyde increases the amount of peracetic acid formed and so will, in turn, cause an increase in the rate of decomposition of this acid (or its radical).

Another interesting fact emerges from the experimental results presented above. In the previous paper we discussed the various mechanisms proposed for the oxidation of acetaldehyde, and though there are disagreements about the exact mechanism, it is generally agreed (Bäckström, *Z. physikal. Chem.*, 1934, *B*, **25**, 115; Lewis and von Elbe, " Combustion, Flames, and Explosions in Gases," Cambridge, 1938; Bodenstein, *Rec. Trav. chim.*, 1940, **59**, 48) that

the acetyl radical plays an important part in the reaction, and that the propagation reactions are :

$$CH_3{\cdot}CO + O_2 = CH_3{\cdot}CO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$CH_3{\cdot}CO_3 + CH_3{\cdot}CHO = CH_3{\cdot}CO_3H + CH_3{\cdot}CO \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

There has, however, been considerable controversy regarding the thermal stability of the acetyl radical. Most of the evidence for its existence and its stability has been obtained in photo-chemical experiments, and the facts have recently been collated and discussed by Steacie (" Atomic and Free Radical Reactions," Reinhold, New York, 1946). Briefly, early evidence (Glazebrook and Pearson, *J.*, 1937, 576; Spence and Wild, *ibid.*, p. 352) appeared to show that acetyl was unstable above 60°. Later, Gorin (*Acta Physicochim., U.S.S.R.*, 1938, **8**, 513; *J. Chem. Physics*, 1939, **7**, 256), from a study of the photolysis of acetone in the presence of iodine vapour, showed that some acetyl iodide was produced at a temperature as high as 140°, and from his results he estimated a minimum value of 17 kcals. for the activation energy of the decomposition $CH_3{\cdot}CO = CH_3 + CO$, which is in excellent agreement with the value of 16 kcals. estimated by Bawn (*Trans. Faraday Soc.*, 1938, **34**, 598) by transition-state theory, and with more recent experimental values (Herr and Noyes, *J. Amer. Chem. Soc.*, 1940, **62**, 2052). Later work by Benson and Forbes (*J. Amer. Chem. Soc.*, 1943, **65**, 1399) threw some doubt on the reliability of some of Gorin's analytical methods, though they do find evidence that the acetyl radical is capable of existence at 100° and above. Gorin's views are, however, supported by the work of Anderson and Rollefson (*ibid.*, 1941, **63**, 816).

Because of the belief that acetyl is unable to exist above 60°, Rice and Schildknecht (*ibid.*, 1938, **69**, 3044) and Walsh (*Trans. Faraday Soc.*, 1946, **42**, 269) have rejected oxidation mechanism involving this radical. Rice and Schildknecht worked on the photo-oxidation of acetone at 80—100°; but though they reject the acetyl radical from consideration, they do not present any compelling experimental evidence for doing so. In any case, their mechanism for the oxidation of acetone can hardly be taken seriously, for it fails to account for the occurrence of carbon dioxide which makes up about 45% of the reaction products.

Consideration of the results presented in Fig. 2, and the general agreement that the peracetic acid is formed in this oxidation by reactions (1) and (2), lead us to the view that the acetyl radical must be sufficiently stable to exist at about 200° long enough to react with oxygen to form the peracetyl radical.

Experiments were carried out by one of us (C. A. McD.), using the sodium-flame technique developed by Bawn and his co-workers (*Trans. Faraday Soc.*, 1938, **34**, 608; 1939, **35**, 185, 889), in an attempt to detect and study the properties of the acetyl radical. Using the reaction $CH_3{\cdot}COCl + Na = NaCl + CH_3{\cdot}CO$ at 300°, we were unable to detect any diacetyl and so concluded that the acetyl radical does not long survive its own collisions at this temperature.

One of us (J. H. T.) thanks the University of Liverpool for a Campbell Brown Fellowship.

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475. *The Reaction of Methyl Radicals with Olefins. Part I. The Temperature Coefficient of the Induced Polymerisation of Ethylene.*

By F. A. RAAL and C. J. DANBY.

When a mixture of acetaldehyde vapour and ethylene is irradiated with ultra-violet light at temperatures between 200° and 350° c., methyl radicals from the aldehyde photolysis induce a chain polymerisation of the olefin. From the temperature coefficient of the reaction the activation energy for the step, $CH_3 + C_2H_4$, is estimated to be 6·8 kcals.

THE rate of photolysis of acetaldehyde vapour by ultra-violet light at temperatures of about 300° is, in general, reduced by addition of olefins, which may undergo induced polymerisation. These reactions have been studied by Danby and Hinshelwood (*Proc. Roy. Soc.*, 1941, *A*, **179**, 169), who showed that they gave a particularly convenient method of following the interactions of methyl radicals with olefins and of investigating the kinetics of the induced polymerisation. The experiments have now been extended and the present paper describes an investigation into the influence of temperature on the methyl-radical-induced polymerisation of ethylene.

Experimental.

Methods.—The experimental methods employed were identical with those used by Danby and Hinshelwood. The mixture of acetaldehyde vapour and olefin was irradiated in a quartz vessel with plane-parallel windows by the unfiltered light from a mercury arc radiating principally at about 3600 A. The reaction vessel was maintained at the required temperature in an electric furnace. The reactions were followed by direct measurement of the overall pressure change on a mercury manometer and by chemical analysis for unchanged acetaldehyde in gas samples by the method of Friedemann, Cotonio, and Shaffer (*J. Biol. Chem.*, 1927, **73**, 342).

Acetaldehyde was dried and carefully fractionated through a long column. Commercial ethylene was dried by passage through P_2O_5 and distilled from a trap cooled in liquid air, only the middle fraction being collected.

Results.—Experiments were made at temperatures between 200° and 350°, within which limits the reactions proceeded at conveniently measurable rates under the experimental conditions employed. At each temperature the rate of photolysis of a constant amount of acetaldehyde (50 mm.) and the rate of polymerisation of the ethylene were measured for a series of ethylene pressures between zero and 400 mm. The amounts of photolysis and of polymerisation were nearly linear with respect to time over the early part of the reaction, and initial rates were therefore obtained by measuring the extent of reaction in a standard period of 8 minutes. When the rate of reaction decreased rapidly with time, the data were plotted and initial rates obtained by drawing tangents. The results are given in Table I.

Table I.

The Effect of Temperature on the Rate of Photolysis of 50 mm. of Acetaldehyde in the Presence of Ethylene, and on the Rate of the Induced Polymerisation.

(Rates are initial rates and are expressed in terms of the number of mm. of gas reacting in 8 minutes.

Initial C_2H_4 pressure, mm.	Rate of photolysis.					Rate of polymerisation.				
	200°.	250°.	300°.	325°.	350°.	200°.	250°.	300°.	325°.	350°.
0	5·3	10·4	16·5	20·2	25·0	—	—	—	—	—
50	4·0	8·5	14·2	17·5	22·3	2·4	4·5	7·3	7·9	8·3
100	3·3	7·5	12·6	15·6	19·9	4·0	8·6	12·3	13·6	14·1
150	2·6	6·8	11·3	13·8	18·3	5·9	11·8	16·3	17·6	19·5
200	2·4	6·2	10·4	13·1	17·1	7·2	14·2	19·8	22·0	23·9
250	2·2	5·7	9·3	11·7	16·0	7·7	15·6	21·6	23·5	27·0
300	1·8	5·0	8·3	10·6	14·4	8·0	17·0	24·4	26·9	31·4
350	—	—	7·6	—	—	—	—	27·0	—	—
400	1·2	4·1	7·0	9·5	12·8	9·0	19·8	29·5	32·5	38·3

Discussion.

Danby and Hinshelwood found that the kinetics of the photolysis of acetaldehyde in the presence of olefin were consistent with the following reaction mechanism:

$CH_3{\cdot}CHO + h\nu$	$= CH_3 + CHO$	k_1	(1)
$CH_3 + CH_3{\cdot}CHO$	$= CH_3 + CH_4 + CO$	k_2	(2)
$CH_3 + CH_3$	= chain ended	k_3	(3)
$CH_3 + C_2H_4$	$= R_1$	k_4	(4)
$R_1 + C_2H_4$	$= R_2$	k_5	(5)
$R_2 + C_2H_4$	$= R_3$	$k_{5'}$	(5′)
$R_{n-1} + C_2H_4$	$= R_n$	k_{5*}	(5*)
R_n	= product + CH_3	k_6	(6)
R_n	= chain ended	k_7	(7)

The usual stationary-state treatment of these equations leads to the expressions for the rate of photolysis of acetaldehyde in the presence of ethylene (ρ), and for the rate of the induced polymerisation (σ), which are given below:

$$\rho = C[CH_3{\cdot}CHO](\{[C_2H_4]^2 + \rho_0^2/C^2[CH_3{\cdot}CHO]^2\}^{\frac{1}{2}} - [C_2H_4]) \quad . \quad . \quad . \quad . \quad . \quad (I)$$

$$\sigma = \tfrac{1}{2}nK[C_2H_4](\{[C_2H_4]^2 + \rho_0^2/C^2[CH_3{\cdot}CHO]^2\}^{\frac{1}{2}} - [C_2H_4]) \quad . \quad . \quad . \quad . \quad . \quad (II)$$

where $C = k_2k_4\beta/2k_3$, $K = (k_4)^2\beta/k_3$, and $\beta = 1 - k_6/(k_6 + k_7)$. n is the average number of ethylene molecules incorporated in the product and ρ_0 is the rate of photolysis of pure acetaldehyde under the conditions of the experiment.

The kinetic chain length of the polymerisation was considerable, but the average molecular weight of the product was small. This was shown to be due to a chain-transfer reaction (reaction 6). The kinetics require that the rate-determining chain-ending step should be unimolecular with respect to the growing polymer radical (reaction 7). This can arise if reaction 7 represents the isomerisation of the radical to a form for which both the addition of further ethylene and the splitting-off of a methyl radical to give chain transfer are unlikely. The precise mechanism of

the eventual fate of the polymer radical—either bimolecular recombination or adsorption and reaction on the vessel wall—would then not affect the kinetics of the main process. The marked diminution in the rate of polymerisation in the series ethylene, propylene, *iso*butylene was shown to be due to increasing ease of this reaction.

FIG. 1.

Effect of temperature on photolysis rate of 50 mm. acetaldehyde in the presence of varying amounts of ethylene. The curves are calculated *from equation* (I) *with the values of the constant* C *given in Table II.*

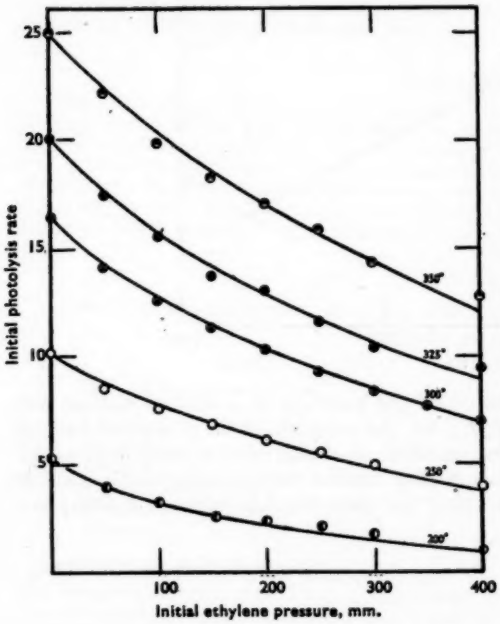


FIG. 2.

Effect of temperature on polymerisation rate of varying amounts of ethylene induced by photolysis of 50 mm. acetaldehyde. The curves are calculated *from equation* (II) *with the values of the constants* C *and* ½nK *given in Table II.*

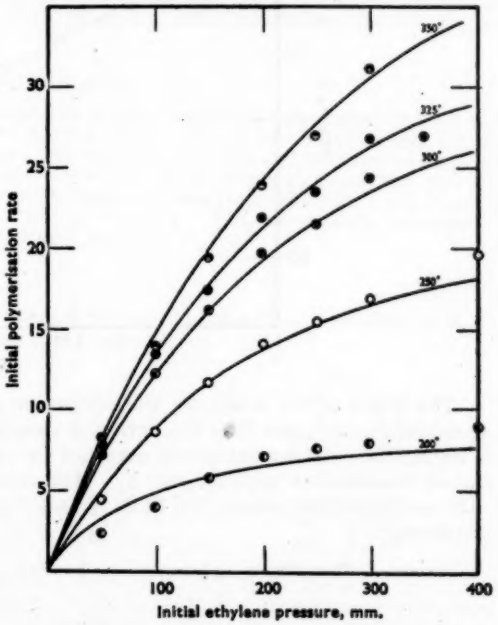


Table II give values of the constants C and $\frac{1}{2}nK$ which, when substituted in equations I and II, give curves in close agreement with the experimental results. Fig. 1 shows the curves obtained in this way for the rate of photolysis of 50 mm. of acetaldehyde at different temperatures as a function of the ethylene pressure. The experimental points are given for comparison. Fig. 2 shows the corresponding results for the polymerisation rate.

TABLE II.

Temp., ° K.	C (× 10⁴).	$\frac{1}{2}nK$ (× 10⁴).	nk_4/k_2.
473	4·82	3·68	0·764
523	6·12	3·62	0·591
573	8·01	3·85	0·481
598	9·24	3·82	0·413
628	10·0	3·58	0·358

In equations I and II, $C = k_2k_4\beta/2k_3$, and $K = (k_4)^2\beta/k_3$. Hence $\frac{1}{2}nK/C = nk_4/k_2$. If n is independent of temperature over the range involved, then

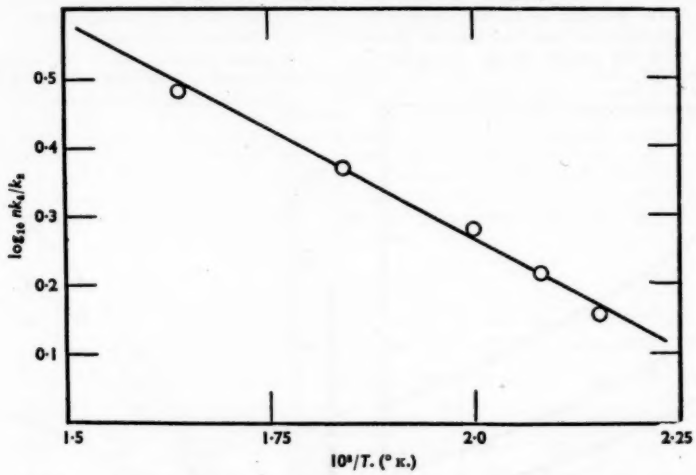
$$\frac{\mathrm{d}\ln(nk_4/k_2)}{\mathrm{d}T} = \left[\frac{\mathrm{d}\ln k_4}{\mathrm{d}T} - \frac{\mathrm{d}\ln k_2}{\mathrm{d}T}\right] = \frac{E_4}{RT^2} - \frac{E_2}{RT^2}$$

where E_4 and E_2 are the activation energies of reactions 4 and 2, respectively. The difference in the activation energy for the reaction of methyl radicals with acetaldehyde and with ethylene may therefore be obtained from the slope of the graph of $log_{10}(nk_4/k_2)$ against the reciprocal of the absolute temperature (Fig. 3). The slope is equal to $-(E_4 - E_2)/2{\cdot}303\boldsymbol{R}$, whence $E_4 - E_2 = -2{\cdot}9$ kcals.

The temperature coefficient of the acetaldehyde photolysis gives a value of 9·7 kcals. for the reaction, $CH_3 + CH_3{\cdot}CHO$ (Mitchell and Hinshelwood, *Proc. Roy. Soc.*, 1937, *A*, **159**, 32; Akeroyd and Norrish, *J.*, 1936, 890). We therefore arrive at the value of 6·8 kcals. for the activation energy of the reaction, $CH_3 + C_2H_4$.

FIG. 3.

Temperature coefficient of the ratio nk_4/k_2.



The value of 9·7 kcals. for the activation energy of the reaction of a methyl radical with acetaldehyde assumes that the activation energy, E_3, for the recombination of methyl radicals is negligible. This assumption may not be quite justified, in which case a correction of $\frac{1}{2}E_3$ should be added to both E_2 and E_4. The conclusion that methyl radicals react with ethylene with an activation energy 2·9 kcals. smaller than that for their reaction with acetaldehyde is unaffected.

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476. *The Reaction of Methyl Radicals with Olefins. Part II. The Comparison of the Reactivity of Different Olefins.*

By F. A. RAAL and C. J. DANBY.

When acetaldehyde vapour is irradiated with ultra-violet light at 300° in the presence of different olefins, the photolysis is inhibited to an extent which increases with increasing molecular weight of the olefin, and more markedly as the number of methyl groups on the olefinic carbon atoms is increased. The rate of polymerisation of the higher olefines is small and becomes independent of olefin pressure as soon as the latter exceeds a small value. The ease of the primary interaction of methyl radicals with olefins does not vary greatly with the nature of the olefin, and the increasing inhibition is due to a greater tendency of the higher olefins to give products which are unable to undergo chain transfer.

DANBY and HINSHELWOOD (*Proc. Roy. Soc.*, 1941, *A*, **179**, 169) investigated the kinetics of the photolysis of acetaldehyde in the presence of ethylene, propylene, and *iso*butylene. Their results have been confirmed and the series of olefins extended to include butene-1, butene-2, trimethylethylene, tetramethylethylene, and hexene-1.

EXPERIMENTAL METHODS.

The experimental arrangements were the same as those described in the preceding paper. All experiments were carried out at 300°. The olefins were prepared as follows.

Propylene.—*iso*Propyl alcohol was dehydrated with phosphoric oxide.

iso*Butylene.*—*tert.*-Butyl alcohol was dehydrated with 30% sulphuric acid (by volume) or by anhydrous oxalic acid.

Butene-1.—This was made by the action of alcoholic potash on *n*-butyl iodide.

Butene-2.—*sec.*-Butyl alcohol was carefully dehydrated with phosphoric oxide.

The above olefins are gases at room temperature and were dried by passage through phosphoric oxide and fractionated between cooled traps, only the middle fractions being collected. Infra-red analysis of the butene-2 showed it to be substantially free from butene-1.

Trimethylethylene.—*tert.*-Amyl alcohol was dehydrated by 50% sulphuric acid (by volume). The distillate was washed with 10% sodium hydroxide and with water, and after being dried ($CaCl_2$) was fractionated (b. p. 36—38°).

Tetramethylethylene.—Methyl *tert.*-butyl ketone was prepared from acetone by way of pinacol hydrate (*Org. Synth.*, Coll. Vol. I, 448) and reduced with sodium to methyl-*tert.*-butylcarbinol (Richard, *Ann. Chim.*, 1910, [viii], **21**, 346), which was then dehydrated with anhydrous oxalic acid. The tetramethylethylene was separated by steam-distillation, dried, and fractionated (b. p. 72—74°).

Hexene-1.—Allyl bromide was added very slowly to a solution of propylmagnesium bromide in dry ether, and after decantation from the solid residue most of the ether was removed by distillation. The remaining ether was eliminated by repeated washing with water, and the olefin dried ($CaCl_2$) and fractionated (b. p. 61—63°) (*J. Amer. Chem. Soc.*, 1918, **40**, 832). Infra-red analysis showed that all the double bonds in the product were terminal.

Experimental Results.

The initial rate of photolysis and the rate of the induced polymerisation were measured at 300° with 50 mm. acetaldehyde and various amounts of the different olefins. Fig. 1 shows the results for the inhibition of the aldehyde photolysis by ethylene, butene-2, trimethylethylene, and tetramethylethylene. Fig. 2 gives the rate of the induced polymerisation as a function of olefin pressure, the marked points in these figures being the experimental values, and the curves being *calculated* from equations I and II of the preceding paper. Similar curves were obtained for the other olefins. The values of the constants C and $\frac{1}{2}nK$ which give the closest agreement with experiment are given in Table I.

Table I.

Values of the constants C *and* $\frac{1}{2}$nK *which give the closest agreement with experiment when substituted in equations I and II.*

Olefin.	C.	$\frac{1}{2}nK$.
Ethylene	$8{\cdot}01 \times 10^{-4}$	$3{\cdot}85 \times 10^{-4}$
Propylene	$1{\cdot}00 \times 10^{-2}$	$7{\cdot}2 \times 10^{-3}$
*iso*Butylene	$1{\cdot}06 \times 10^{-2}$	$6{\cdot}6 \times 10^{-3}$
Butene-1	$1{\cdot}10 \times 10^{-2}$	$8{\cdot}0 \times 10^{-3}$
Butene-2	$1{\cdot}12 \times 10^{-2}$	$6{\cdot}3 \times 10^{-3}$
Trimethylethylene	$1{\cdot}65 \times 10^{-2}$	$6{\cdot}0 \times 10^{-3}$
Tetramethylethylene	$2{\cdot}24 \times 10^{-2}$	$1{\cdot}0 \times 10^{-2}$
Hexene-1	$1{\cdot}15 \times 10^{-2}$	$3{\cdot}0 \times 10^{-3}$

The values for ethylene and propylene are in good agreement with those obtained by Danby and Hinshelwood (*loc. cit.*). The extent of the inhibition of the acetaldehyde photolysis by *iso*butylene was somewhat less than that previously observed. The values given above were obtained with several different samples of *iso*butylene and are probably more reliable.

Discussion.

The reaction scheme given in the preceding paper for the photolysis of acetaldehyde in the presence of ethylene leads to equations for the rate of photolysis of the aldehyde (equation I) and for the rate of the induced polymerisation (equation II). The results in Figs. 1 and 2 show that, with suitable choice of constants, these equations also give excellent agreement with the experimental results for the photolysis of acetaldehyde in the presence of the higher olefins, suggesting that the same reaction mechanism adequately describes these reactions. Quantitative information about the relative values of the velocity constants of the individual reactions with different olefins may be derived from the values of the constants given in Table I.

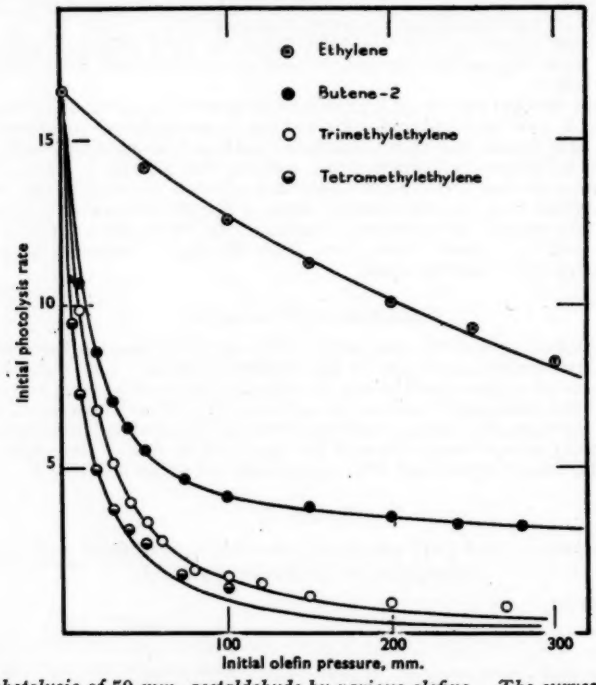
Danby and Hinshelwood showed that for ethylene the value of the constant n was approximately 3; with the higher olefins no great error is introduced by assuming a standard value $n = 2$ for these reactions. From the values of C and $\frac{1}{2}nK$ in Table I we can then calculate a series of values for the ratio k_4/k_2 for:

$$C = k_2k_4\beta/2k_3, \text{ and } K = (k_4)^2\beta/k_3$$

whence $K/2C = k_4/k_2$.

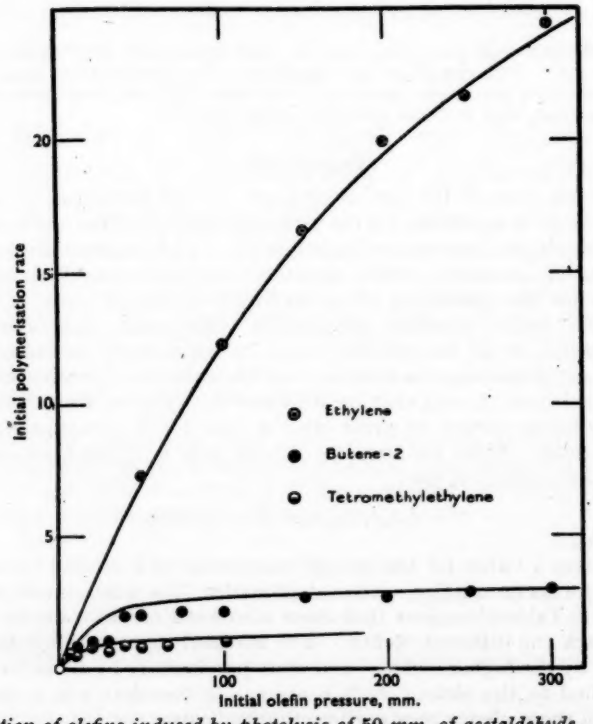
The ratio k_4/k_2 gives a value for the ease of interaction of a methyl radical with the olefin, compared with that for its interaction with acetaldehyde. The relatively small differences in the value of k_4/k_2 shown in Table II suggest that there are no major variations in the ease with which methyl radicals attack the different olefins. The markedly greater inhibition of the aldehyde photolysis produced by the higher olefins—and more particularly by those having more than one methyl group attached to the olefinic carbon atoms—is therefore not to be attributed to an increased tendency of these olefins to absorb methyl radicals.

FIG. 1.



Inhibition of the photolysis of 50 mm. acetaldehyde by various olefins. The curves are those calculated *from equation I with the values of* C *given in Table I.*

FIG. 2.



Rates of polymerisation of olefins induced by photolysis of 50 mm. of acetaldehyde. The curves are those calculated *from equation II with the values of* C *and* $\frac{1}{2}$nK *given in Table I.*

From the expressions for C and K given above, $\beta = \frac{4 k_3 C^2}{(k_2)^2 K}$. Values of β, and hence of the ratio k_7/k_6 may be obtained from this expression by the method used by Danby and Hinshelwood.

TABLE II.

Olefin.	k_4/k_2.	β.	k_7/k_6.
Ethylene	0·16	0·055	0·06
Propylene	0·36	0·30	0·43
*iso*Butylene	0·31	0·37	0·59
Butene-1	0·36	0·33	0·49
Butene-2	0·28	0·43	0·75
Trimethylethylene	0·18	0·98	49·0
Tetramethylethylene	0·22	1·0	∞
Hexene-1	0·13	0·95	19·0

(Because of the very small extent of polymerisation observed with tri- and tetra-methylethylene the value of the constant $\frac{1}{2}nK$ for these olefins is known to a rather lower degree of precision. The corresponding data in the above table are shown bracketed.)

This requires an estimate of the chain length of the photolysis of acetaldehyde under the conditions of the experiment. By extrapolation from the results of Mitchell and Hinshelwood (*Proc. Roy. Soc.*, 1937, *A*, **159**, 32) a reasonable value for the chain length of photolysis of 50 mm. acetaldehyde at 300° is found to be 28 units. From this value, together with the data in Table I the approximate values for β and for k_7/k_6 given in Table II are obtained.

Several interesting conclusions may be drawn at once from these results. As explained above, the small variation in the value of the ratio k_4/k_2 in passing from ethylene to the higher olefins shows that the higher olefins do not in general react more readily with methyl radicals. On the other hand there is a striking increase in the value of the ratio k_7/k_6. This ratio gives a measure of the relative probability that a growing polymer radical should undergo chain termination rather than chain transfer. Whilst with ethylene only about one reaction chain in 20 fails to undergo chain transfer and regenerate a methyl radical, with the higher olefins there is only a small probability that chain transfer will occur.

The pronounced inhibition of the acetaldehyde photolysis produced by the more complex olefins is therefore to be attributed to the increasing tendency of the larger radicals to isomerise into a form which is unable either to continue the polymerisation by addition of fresh olefin molecules or to continue the kinetic chain by the process of methyl-radical chain transfer.

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477. *The Reaction of Methyl Radicals with Olefins. Part III. Reaction with Mixtures of Ethylene and Higher Olefins.*

By F. A. RAAL, C. J. DANBY, and SIR CYRIL HINSHELWOOD.

Addition of ethylene to higher olefins antagonises the inhibitory action which these exert on the photolysis of acetaldehyde. This is due to an increased possibility of chain transfer; radicals derived from the higher olefins add on C_2H_4 and regenerate CH_3 groups under conditions where they would normally isomerise and therby terminate the chain.

THE rates of polymerisation under the influence of methyl radicals from acetaldehyde being known from previous work for ethylene and propylene separately, and the effect of these two gases in inhibiting the photolysis of the aldehyde having been measured, an obvious extension of the investigation was to study the behaviour of mixtures of the two.

The experimental methods were those already described. All experiments were carried out at 300° c. with an initial acetaldehyde pressure of 50 mm. The rate of photolysis of the aldehyde was measured as a function of the composition of the binary ethylene–propylene mixture, and the total rate of consumption of olefin determined at the same time.

The results are shown in Figs. 1—4.

The most significant effects of mixing the two olefins are:

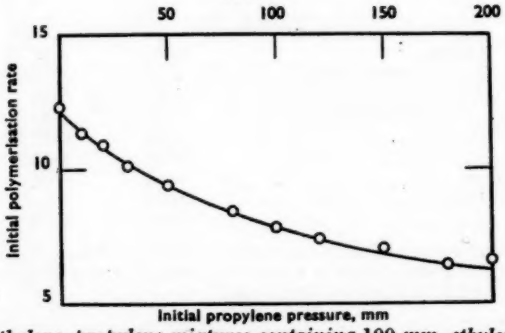
(1) The rates of polymerisation are far from additive (Figs. 1 and 2).

(2) With a constant ethylene pressure the addition of propylene causes a steep decrease in the rate of photolysis (Fig. 3).

(3) With constant propylene pressure, however, the addition of the first amounts of ethylene

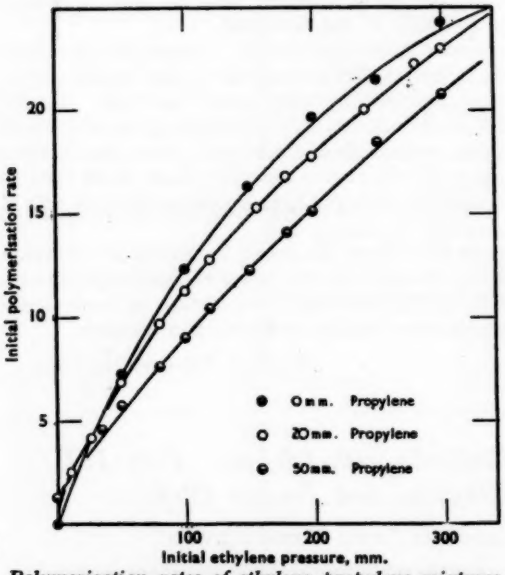
causes an increase in the photolysis rate, that is, the ethylene, although itself an inhibitor, antagonises the effect of the propylene (Fig. 4).

FIG. 1.



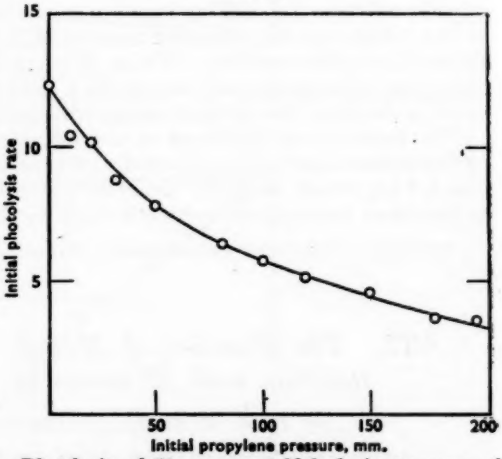
Polymerisation rate of ethylene–propylene mixtures containing 100 *mm. ethylene and various propylene pressures. Marked points are experimental. Curve is calculated from equation IV.*

FIG. 2.



Polymerisation rates of ethylene–propylene mixtures as function of ethylene pressure. Marked points are experimental. Curve is calculated from equation IV.

FIG. 3.



Photolysis of 50 *mm. acetaldehyde in presence of* 100 *mm. ethylene and various propylene pressures. Curve is calculated from equation III.*

The theoretical treatment of these effects is somewhat complicated, and we may approach it in the following way.

The reactions written below will be expected to occur from what is known of the behaviour of the individual gases.

1.	$CH_3{\cdot}CHO + h\nu = CH_3 + CHO$	k_1
2.	$CH_3{\cdot}CHO + CH_3 = CH_3 + CH_4 + CO$	k_2
3.	$CH_3 + CH_3 = C_2H_6$	k_3
4.	$CH_3 + C_2H_4 = R_e$	k_4^e
	$CH_3 + C_2H_3 = R_p$	k_4^p
5.	$R_e + C_2H_4 = R_{ee}$	k_5^{ee}
	$R_p + C_2H_3 = R_{pp}$	k_5^{pp}
	$R_{ee} + C_2H_4 = R_{eee}$	k_5^{eee}
6.	$R_{eee} =$ product $+ CH_3$	k_6^{eee}
	$R_{pp} =$ product $+ CH_3$	k_6^{pp}
7.	$R_{eee} =$ product (chain ended)	k_7^{eee}
	$R_{pp} =$ product (chain ended)	k_7^{pp}

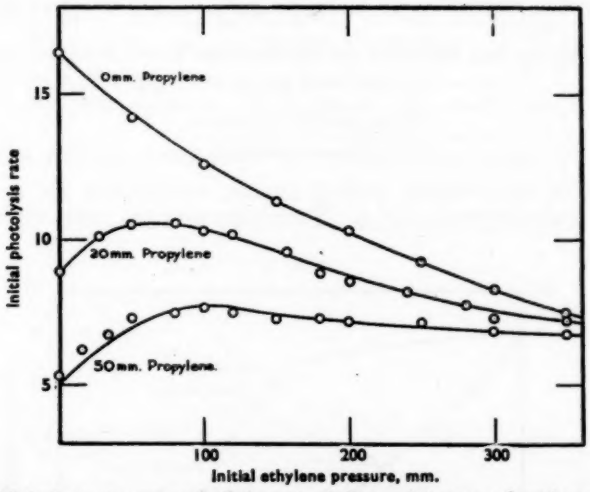
Here the polymerisation is assumed to proceed to the same degree as with the separate gases.

Additional steps rendered possible by the presence of both olefins simultaneously are:

$$(a)\ R_e + C_3H_6 = R_{ep}$$
$$(b)\ R_p + C_2H_4 = R_{pe}$$
$$\ldots\ldots\ \text{etc.}$$

in a rather complex array.

FIG. 4.



Photolysis of acetaldehyde in presence of ethylene–propylene mixtures as function of ethylene pressure. Curves are calculated from equation III.

Before adding these to the set numbered 1—7, we may make a preliminary investigation in an indirect manner. Let a given ethylene–propylene mixture be regarded as equivalent to a single olefin of appropriate properties. Its behaviour should then be describable by a series of terms such as the above in which the letters with the subscript p or those with the subscript e are omitted. The rates of polymerisation, σ, and of photolysis, ρ, will then be given as in the earlier investigations by

$$\sigma = \tfrac{1}{2}nK[X](\{[X]^2 + \rho_0^2/C^2[CH_3{\cdot}CHO]^2\}^{\frac{1}{2}} - [X]) \quad \ldots\ldots\ (I)$$

and

$$\rho = C[CH_3{\cdot}CHO](\{[X]^2 + \rho_0^2/C^2[CH_3{\cdot}CHO]^2\}^{\frac{1}{2}} - [X]) \quad \ldots\ldots\ (II)$$

where $[X]$ = concentration of "olefin,"
ρ_0 = photolysis rate in absence of olefin,
$C = k_2k_4\beta/2k_3$, $K = k_4^2\beta/k_3$,
$\beta = k_7/(k_6 + k_7)$
and n = average number of olefin molecules added before the chain ends.

β is the characteristic measure of the probability that the chain ends, whilst $(1 - \beta)$ is that of chain transfer.

For the fictitious "olefin" of the mixture we now determine β and plot it as a function of composition for mixtures in which the total pressure is kept constant. Since n varies from 3 for ethylene to 2 for propylene, a linear interpolation is taken for the mixtures. In this way the graph shown in Fig. 5 is obtained.

We may now consider what form this graph would be likely to have if the interpolymerisation of the ethylene and propylene were random. Suppose at a given step of the chain the probability of addition of ethylene to a growing radical is r and that of the addition of propylene w. Suppose further that after the addition of three successive molecules of ethylene there is a very high probability of chain transfer, according to a reaction of the type characterised above by the constant k_6, and that after the addition of two successive propylene molecules there is a high probability of chain ending. These assumptions are suggested by the results found with the individual gases. The chain may now end in many ways: for example, after the addition of two propylenes alone; after the addition of ethylene, propylene, ethylene, propylene, propylene;

and so on. The total probability of ending (rather than transfer) is given by a convergent series of which the earlier terms are:

$$w^2(1 + r + r^2 + wr + 2wr^2 + 2wr^3 + w^2r^3 + 3w^2r^3 + wr^4 + 4w^2r^4 + w^3r^3 + 3w^2r^5 + 4w^3r^4 + 7w^3r^5 + w^2r^6 + w^4r^4 \ldots\ldots).$$

Now since it is known from previous work that there is a much greater difference between different olefins than between different radicals in respect of the same olefin, it is not unreasonable to estimate r and w from the known rates of reaction of methyl radicals with ethylene and propylene, respectively. k_4 for propylene is 2·2 times as great as for ethylene.

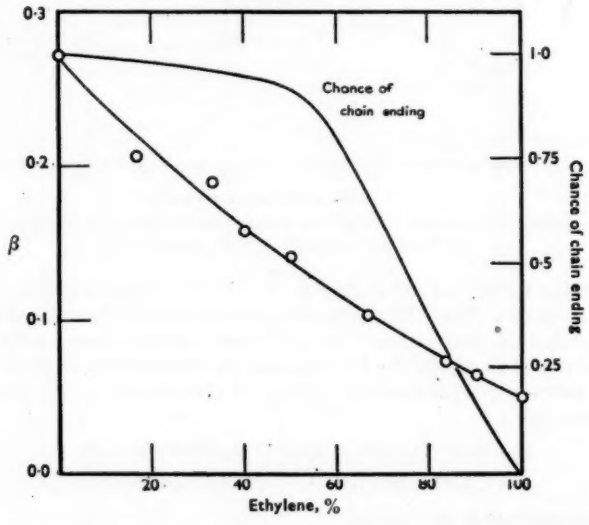
Thus $$w/[C_3H_6] \div r/[C_2H_4] = 2{\cdot}2$$

whence $$w = 2{\cdot}2/(2{\cdot}2 + x) \text{ and } r = x/(2{\cdot}2 + x)$$

where $$x = \frac{\text{ethylene concentration}}{\text{propylene concentration}}.$$

The probability of chain-ending plotted against composition for a series of ethylene–propylene mixtures is also shown in Fig. 5. The values obtained range necessarily from unity to

FIG. 5.



zero, since no transfer was allowed for with propylene and no ending with ethylene, though in fact β varies from 0·055 with ethylene to 0·30 with propylene. Nevertheless, the general shapes of the curves for the probability of chain-ending according to the above calculation and for the variation of β should be similar if the assumptions are generally correct.

Comparison of the curves in Fig. 5, however, shows that some quite special factor is operative. According to the calculation just made, the probability of chain-ending should decrease only very slowly as the composition changes from pure propylene by addition of ethylene, and should not show a serious fall until about 50% of the latter is present. In fact β decreases rapidly with the first additions of ethylene. It seems clear, therefore, that the ethylene has a very marked specific effect in preventing chain-ending. This is reflected in its action in antagonising the inhibitory effect of the propylene on the photolysis.

Since this effect now appears as a major factor in the observed behaviour, we express it by the following equation:

$$8.\ R_{pp} + C_2H_4 = \text{product} + CH_3 \qquad k_8$$

R_{pp} is assumed to regenerate a methyl radical if it meets ethylene before it has time to isomerise and become inactive.

This last equation is now added to the set 1 . . . . . 7.

The question now arises as to the part played by the reactions labelled (*a*), (*b*) . . . . . above.

As far as the photolysis rate is concerned they will play little part, the inhibitory action being principally determined by the competition of the reactions numbered 6, 7, and 8.

Ignoring, therefore, (*a*), (*b*) . . . . , and solving the usual stationary state equations for the reactions characterised by k_1 to k_8, we obtain for the photolysis rate:

$$\rho = C[CH_3{\cdot}CHO]\left[\left\{\left([C_2H_4] + \frac{W[C_3H_6]}{1 + S[C_2H_4]}\right)^2 + \frac{\rho_0^2}{C^2[CH_3{\cdot}CHO]^2}\right\}^{\frac{1}{2}} - \left([C_2H_4] + \frac{W[C_3H_6]}{1 + S[C_2H_4]}\right)\right] . \quad \text{(III)}$$

where $C = k_2k_4^{e}\beta^{e}/2k_3$, $W = k_4^{p}\beta^{p}/k_4^{e}\beta^{e}$,

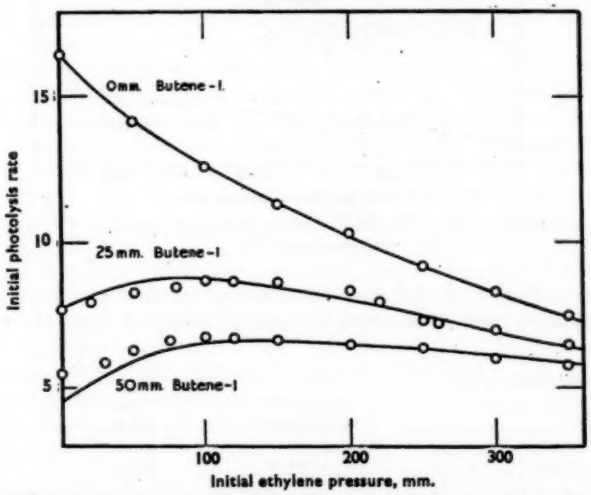
and $S = k_8/(k_6^{p} + k_7^{p})$.

C and W are known from the measurements on ethylene and propylene alone, whilst S must be determined from the experiments themselves.

Figs. 3 and 4 show that equation III expresses the results for the photolysis rates satisfactorily.

In considering the polymerisation rates the matter is less simple.

FIG. 6.



Photolysis of acetaldehyde in presence of ethylene–butene-1 mixtures. Curves are calculated from equation III.

Fig. 1 shows that for high proportions of propylene the reaction rate is low in any case. Most of the contribution to σ in a mixture comes from the ethylene. As far as the rate goes the influence of the terms derived from (*a*), (*b*) . . . will be small. These reactions may exert some influence but not a very large one, since the value of n is always small.

The polymerisation rate derived from equations 1—8 alone is given by:

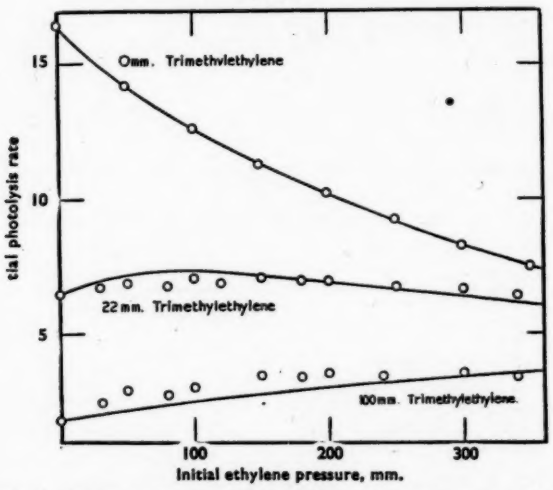
$$\begin{aligned}\sigma &= n^{e}k_4^{e}[CH_3][C_2H_4] + n^{p}k_4^{p}[CH_3][C_3H_6] \\ &= \tfrac{1}{2}n^{e}K\{[C_2H_4] + \delta[C_3H_6]\}\left[\left\{\left([C_2H_4] + \frac{W[C_3H_6]}{1 + S[C_2H_4]}\right)^2 + \frac{\rho_0^2}{C^2[CH_3{\cdot}CHO]^2}\right\}^{\frac{1}{2}}\right. \\ &\qquad \left. - \left([C_2H_4] + \frac{W[C_3H_6]}{1 + S[C_2H_4]}\right)\right] . \quad . \quad \text{(IV)}\end{aligned}$$

where $\delta = n^{p}k_4^{p}/n^{e}k_4^{e}$, and $K = (k_4^{e})^2\beta^{e}/k_3$.

Now n_p is approximately 2 and n_e approximately 3. This would give $\delta = 1{\cdot}5$. In the mixed system δ will be modified, and it seems quite likely that an empirical modification will be enough to express the changed kinetics. In fact if the above equation is tested with $\delta = 0{\cdot}45$, quite an adequate representation of the results is possible, as is shown in Figs. 1 and 2. That δ is below the value calculated above is probably to be attributed to the extra consumption of ethylene in the new chain-transfer step 8. However, the conditions of the experiment are far less suitable for the drawing of detailed conclusions about the polymerisation than they are for the study of the reactions of the radicals from the aldehyde with the mixed olefins.

Similar experiments were made on mixtures of ethylene with butene-1, butene-2, and trimethylethylene respectively. The results were generally in conformity with those described for the ethylene–propylene system, the most significant effect being the antagonism by small amounts of ethylene of the strong inhibitory action of the higher olefins on the photolysis of the aldehyde (see Figs. 6 and 7).

FIG. 7.



Photolysis of acetaldehyde in presence of ethylene–trimethylethylene mixtures. Curves are calculated from equation III.

The values of β are reproduced with the constants shown in the table, C and W being found from experiments with the pure gases, and S being determined from the experiments with a single mixture.

Mixture of ethylene with :	C.	W.	S.
Propylene	8×10^{-4}	12·0	$1{\cdot}65 \times 10^{-2}$
Butene-1	8×10^{-4}	13·0	$1{\cdot}02 \times 10^{-2}$
Butene-2	8×10^{-4}	14·0	$7{\cdot}0 \times 10^{-3}$
Trimethylethylene	8×10^{-4}	19·0	$6{\cdot}6 \times 10^{-3}$

The effectiveness of the chain transfer which occurs where a radical of the type R_{xx} reacts with ethylene decreases, but not at all markedly, with increasing complexity of the olefin.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, February 1st*, 1949.]

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478. *Keto–Enol Ratios in Solutions of Ethyl Acetoacetate. Infra-red Spectroscopic Indications.*

By R. J. W. LE FÈVRE and H. WELSH.

The spectrum of ethyl acetoacetate has been studied in the 3-μ. and 6-μ. regions in relation to the effects of solvent and concentration. Optical density measurements, at the wave-length of maximum absorption due to the C=C linkage, are reconcilable with Meyer's results by the " bromine-titration " method. Estimates are made of the ketone : enol proportions of the ester in ethylene dibromide and pyridine.

IN relation to dielectric-polarisation measurements already presented (Le Fèvre and Welsh, this vol., p. 1909), a consideration of the infra-red spectrum of ethyl acetoacetate became of obvious interest. It is well known that hydroxyl groups and olefinic double bonds, both characteristic of enols, usually cause absorption from 2·7 to 3 μ. and at about 6 μ., respectively (Thompson, *J.*, 1948, 328). The " free-hydroxyl " bands should therefore occur at a region likely to be transparent for the keto-structure, $Me{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et$. The possibility thus existed that enol : ketone ratios could be determined by direct spectral measurement of the enol content of a given equilibrium.

The principles underlying this have been discussed before (Davies and Sutherland, *J. Chem. Physics.*, 1938, **6**, 755, 767; Fox and Martin, *Trans. Faraday Soc.*, 1940, **36**, 902; Thompson and Sutherland, *ibid.*, 1945, **41**, 199). If the optical density (d_λ) at a wave-length λ is taken as log 100/(100−A), where A = % absorption, then for a mixture d_λ is often equal to ($c_E \cdot e_E + c_K \cdot e_K$) × cell length ($c$ refers to the molar concentrations, e to the extinction coefficients of the solutes, and subscripts E and K to the enol and ketone, respectively). Use of a wave-length for which, say, $e_K = 0$, gives $d_\lambda = c_E \cdot e_E$.

Preliminary observations on ethyl acetoacetate in the 2·5—3-μ. region, made with a Hilger D209 spectrograph and quartz prism, have been mentioned by Hukins and Le Fèvre (this vol., p. 898). Absorptions were reported at 2·70 and 2·89—2·90 μ. The former, it was thought, might have been due to traces of water (compare Fox and Martin, *loc. cit.*, on benzyl alcohol, and Davies, *Trans. Faraday Soc.*, 1940, **36**, **333**, on chloral hydrate), and the latter to *cis*-hydroxyl (compare Davies, *loc. cit.*; Wulf *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 2287; Rodebush *et al.*, *ibid.*, 1947, **69**, 770). However, the ester showed no marked absorption at 3·1—3·2 μ. (as do simple alcohols and phenols, or salicylaldehyde) where evidence of intra- and inter-molecular H bonding is to be expected (cf. Fox and Martin, *loc. cit.*; Thompson, *loc. cit.*; Hukins and Le Fèvre, *loc. cit.*).

Previous investigations, of both the infra-red and Raman spectra of ethyl acetoacetate, are on record. Bawn (*J.*, 1932, 1189) had found absorption at 2·9 μ. but had associated it with the C=O group. Barnes and co-workers [*Ind. Eng. Chem.* (*Anal.*), 1943, **15**, 659; "Infra-red Spectroscopy," Reinhold, 1944] include a curve for this ester, between the limits 5 and 10 μ., among their compilations of spectra. It shows a great reduction of transmission between 1700 and 1800 cm.$^{-1}$ and a lesser one between 1600 and 1700 cm.$^{-1}$. The second feature is present also with the esters of fumaric and maleic acids, but not with those of succinic acid, whilst the first is common to all esters. The weaker absorption cited seems therefore to indicate the presence of a C=C linkage. Kohlrausch and Dadieu (*Ber.*, 1930, **63**, 1657; Kohlrausch, "Der Smekal–Raman Effekt," Springer, 1931; *J. Opt. Soc. Amer.*, 1931, **21**, 286; cf. Hibben, "The Raman Effect," Chem. Catalog Co., 1939) have reported the Raman spectrum of ethyl acetoacetate and identified certain shifts with C=O and C=C linkages, although the band at 3380 cm.$^{-1}$ (hydroxyl, 2·96 μ.) seems to have been very faint (it was not detected by Venkateswaran and Bhagavantam, *Indian J. Physics*, 1930, **5**, 129).

The present paper therefore deals with two questions: (*a*) are the OH and C=C absorptions found in the positions and forms to be expected and, if so, (*b*) can their intensities be related to the enol : ketone ratios determined by other methods?

Experimental.

Materials were dried and purified as described by Le Fèvre and Welsh (*loc. cit.*). The spectroscopical examinations were carried out with the Perkin Elmer recording instrument in the Division of Industrial Chemistry, Melbourne (whose hospitality we gratefully acknowledge).

Results are indicated in the figures.

Figs. 1—3 cover the region where hydroxyl frequencies should be displayed, and Figs. 4 and 5 that where C=C and C=O bands are expected. Concentrations are indicated as v/v%.

Discussion.

It will be noted that the curves in carbon tetrachloride reveal an absorption at about 3370 cm.$^{-1}$ (*i.e.*, 2·97 μ.). In carbon disulphide this appeared at approximately 3420 cm.$^{-1}$ (*i.e.*, 2·92 μ.). With the lithium fluoride prisms, the corresponding point was registered rather weakly at *ca.* 3480 (*i.e.*, 2·87 μ.). Hukins and Le Fèvre using a quartz prism recorded it as 3450—3460 cm.$^{-1}$ (*i.e.*, between 2·89 and 2·90 μ.). The absence of *two* absorptions having the relative positions and magnitudes usually reported for OH seems therefore to be established. The single band noted might, of course, represent that normally expected on the long-wave side of, and close to, the "monomeric" hydroxyl band (Fox and Martin, *Proc. Roy. Soc.*, 1937, *A*, **162**, 419, and other references above). If such were the case, we must infer that there is no "free hydroxyl" in the enol form. Yet, in salicylaldehyde (where internal chelation is indicated by evidence of various kinds, Sidgwick and Callow, *J.*, 1924, **125**, 527, and which, like enolic ethyl acetoacetate, contains the structural unit HO—C=C—C=O) the "monomeric" peak is clear at 2·76 μ.—almost the figure given for it by Fox and Martin—notwithstanding the particularly strong and extensive "association" absorption that continues on from this point right into the C–H region (Hukins and Le Fèvre, *loc. cit.*). Because of the last contrast, and in spite of the obvious suggestion provided by the discussion of Buswell, Rodebush, and

Whitney (*J. Amer. Chem. Soc.*, 1947, **69**, 770) on the infra-red spectra of certain vinyl alcohols stabilised against tautomeric rearrangement by steric hindrance from substituent groups, we hesitate to relate the absorptions observed by us to a *cis*-enolic structure of ethyl acetoacetate. The possibility that they might be weak overtones or combinations of the C=C fundamental

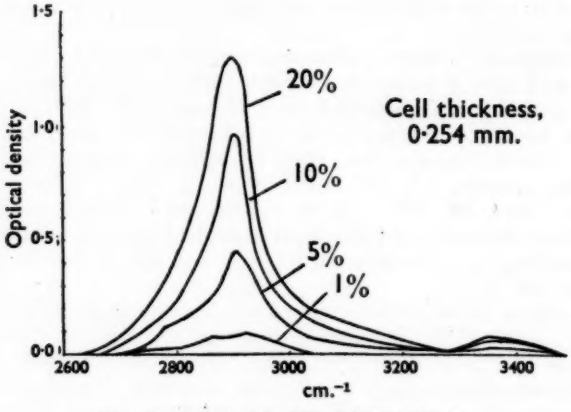

FIG. 1. *Solution in* CCl_4 (NaCl *prism*).

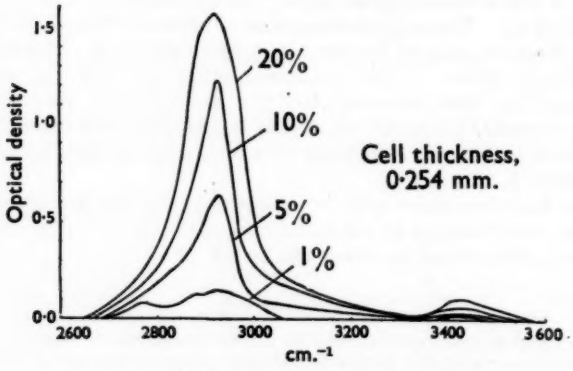

FIG. 2. *Solution in* CS_2 (NaCl *prism*).

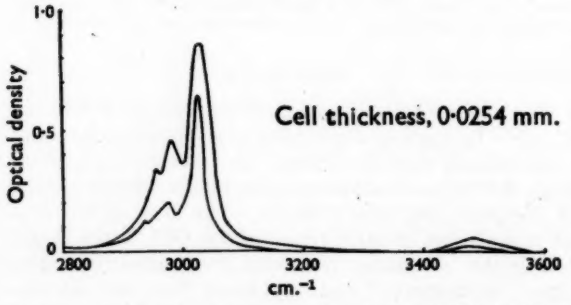

FIG. 3. *Upper curve: pure ester. Lower curve: solution* (20%) *in* CS_2 (LiF *prism*).

cannot be definitely eliminated at this stage (compare Thompson and Whiffen, *J.*, 1946, 1005, on a similar problem with dimeric keten).

The peaks shown in the neighbourhood of 3000 cm.$^{-1}$ in Figs. 1—3, and by Hukins and Le Fèvre, are obviously from C–H stretching modes (Thompson, *loc. cit.*) and require no comment.

When we turn to the 6 μ. region (Figs. 4 and 5), absorption is seen to occur at almost the same wave-lengths in either carbon tetrachloride or carbon disulphide, that at 1640 cm.$^{-1}$ being weaker

than that at 1730 cm.$^{-1}$. The agreement with the diagram of Barnes *et al.* (*loc. cit.*) is satisfactory. For the reason given before, we identify the 1640-cm.$^{-1}$ maxima with the C=C linkage, and those at 1730 cm.$^{-1}$ with superimposed carbonyl and carbethoxy-frequencies. Raman spectra (see above) confirm this, since all esters give displacements which are similar to those of ketones, whilst that of the olefinic double bond is distinct at 1645 cm.$^{-1}$ (Dadieu and Kohlrausch, *Monatsh.*, 1930, **55**, 201).

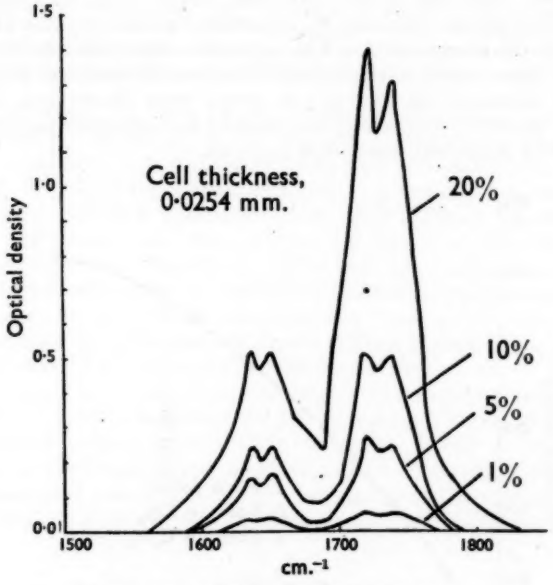

FIG. 4. *Solution in* CCl_4 (NaCl *prism*).

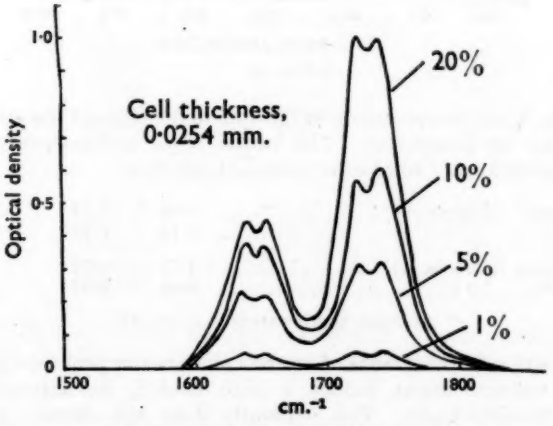

FIG. 5. *Solution in* CS_2 (NaCl *prism*).

For our attempts at quantitative analysis, owing to the poor resolution of the 3400 cm.$^{-1}$ bands by the sodium chloride or lithium fluoride prisms, we have used the wave-lengths of maximum C=C absorption. It is relevant to mention that we think the twin peaks of Figs. 4 and 5 may be adventitious and due to the fact that it was necessary to secure a pen record for the absorption by the cell plus solvent above that for the cell plus solution *on the same paper*, and to use as zero reference the straight line joining the initial and final points *with the shutter closed*. Our experience was, unfortunately, that two " blank " curves could not be matched in this way, departures being correlated roughly with the amount of water-vapour absorption, and tending—

in the final %-transmission graph—to produce small peaks where none should occur. Accordingly, in what follows we have taken mean values of the highest optical densities and in all cases the average of a number of determinations.

We have followed a procedure parallel to that adopted with the apparent-dipole-moment data (Le Fèvre and Welsh, *loc. cit.*) and plotted the observed optical densities for the 1650-cm.$^{-1}$ band against the enol concentrations in g.-mols. per litre in the various solutions (cf. Figs. 4 and 5). The last information was deduced from the " bromine-titration " experiments of Meyer and Kappelmeier (*Ber.*, 1911, **44**, 2718; 1912, **45**, 2852). Our solutions were made up by volume and expressed as weight fractions by assuming that the volume of the solution was the sum of the volumes of the components. This approximation was tested on data obtained in the polarisation work, from which it was evident that weight fractions could be thus calculated with the accuracy of reading of an enol-%—w_1 graph from Meyer and Kappelmeier's results. The fact that Fig. 6 smoothly represents our present findings provides further support for the correctness of the earlier (chemical) keto–enol analyses.

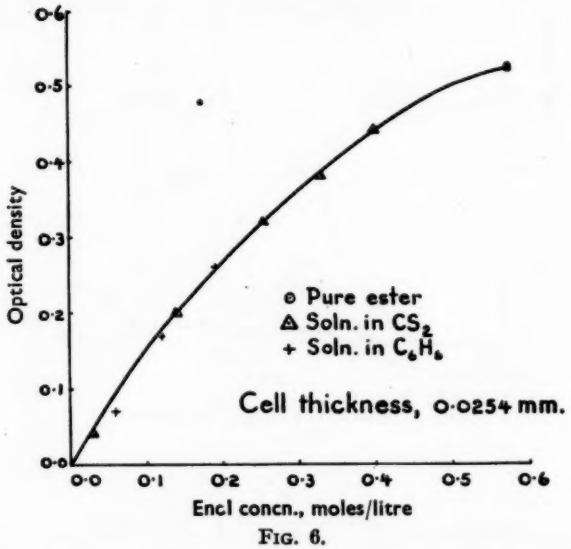

FIG. 6.

With the aid of Fig. 6, an interpretation of the optical densities of the ethylene dibromide and pyridine solutions may be attempted. The ratios K (= enol-concentration/ketone-concentration) against concentrations of total ester obtained are then :

Ethylene dibromide	Concn. (g.-mols./l.)	2·62	1·57	0·786	0·650	0·393
	K *	0·13	0·12	0·10	0·08$_5$	0·08
Pyridine	Concn. (g.-mols./l.)	1·54	0·77			
	K *	0·05	0·05			

* At room temperature, *i.e.*, *ca.* 18°.

The equilibrium position in pyridine is of interest since in our previous paper we left open the possibility that this solvent might induce a high enol-% by intermolecular H-bonding; $C_5H_5N \ldots H \ldots O{-}CMe{:}CH{\cdot}CO_2Et$. This evidently does not occur; presumably therefore the polarity of the medium ($\mu_{C_5H_5N} = 2{\cdot}1$D.; $\varepsilon = ca.$ 12·4) is still the determining influence (cf. Le Fèvre and Welsh, *loc. cit.*).

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479. *Effects of Solvents on the Thermal Interconversion of the Piperonaldoximes.*

By R. J. W. Le Fèvre and (Miss) J. Northcott.

The rates of isomerisation of piperonaldoxime, m. p. 144°, to that of m. p. 112°, have been studied dilatometrically in seven media, each at two temperatures. Energies of activation and frequency factors are calculated and discussed in relation to solvent properties. An empirical expression, $E_{observed} = 24{\cdot}5 + 2{\cdot}7 \log_{10} \mu_{solvent}$, is found to correlate the results satisfactorily. Comparisons are made with analogous data for systems containing –C=C– and –N=N–. The dipole moments of the two oximes are found to be $1{\cdot}5_5$ and $1{\cdot}7_5$ D., respectively.

In a previous paper (this vol., p. 944) on the kinetics of geometrical change of the –N=N– group we noted the paucity of data for related C=C- or C=N-containing systems in the dissolved condition. Certain oxime-inversion studies by Patterson and collaborators (*J.*, 1907, **91**, 504; 1908, **93**, 1941; 1912, **101**, 26, 2100; 1941, 606) were on record, it is true, but these had the disadvantage that, being obtained polarimetrically, they involved media which were always *mixtures* rich in ethyl tartrate. Our observations, for which we desired to find comparisons, had been made in *single* solvents. Moreover, only in the case of piperonaldoxime had Patterson *et al.* (*loc. cit.*, 1908) determined reaction constants at different temperatures, but from these we had found that A and E (in the usual Arrhenius equation) could not be evaluated with satisfactory certainty. We accordingly decided to reinvestigate the last change in several of the liquids used by us for the diazocyanides (Le Fèvre and Northcott, *loc. cit.*).

Dipole Moments of the Isomeric Piperonaldoximes.—The measurements recorded in Table I were made to ascertain whether changes in dielectric constant would be adequate for following the spontaneous (thermal) isomerisation of the oxime of m. p. 144° to that of m. p. 112°. The solutes were prepared by the methods indicated by Patterson and McMillan (*loc. cit.*, 1908).

Experimental procedures and symbols, etc., are as defined in earlier papers (*e.g.*, *J.*, 1937, 1805; this vol., p. 333), the solvent being benzene, and the temperature 25°.

Table I.

$10^6 \times w_1$.	$\varepsilon_{1000\ Kc.}^{25}$.	d_4^{25}.	$\alpha\varepsilon_2$.	βd_2.
0	2·2725	0·87378	—	—
		Labile oxime, m. p. 144°.		
802·0	2·2738	0·87402	1·64	0·301
1,789·0	2·2755	0·87436	$1{\cdot}67_5$	0·323
2,057·9	2·2760	0·87433	1·70	0·269
2,582·0	2·2767	$0{\cdot}87458_5$	1·63	0·312
3,044·3	2·2776	0·87470	$1{\cdot}67_5$	0·301
		Stable oxime, m. p. 112°.		
2,388·3	2·2769	0·87433	1·90	0·237
3,182·7	2·2791	0·87454	2·07	0·240
5,530·0	2·2833	0·87504	1·96	0·228
9,169·7	2·2908	0·87594	$1{\cdot}99_5$	0·240
13,376·0	2·2982	0·87703	1·92	0·243

Since the α and β factors display no signs of smooth concentration dependence (contrast Calderbank and Le Fèvre, this vol., p. 1462) polarisations are computed from the arithmetic means:

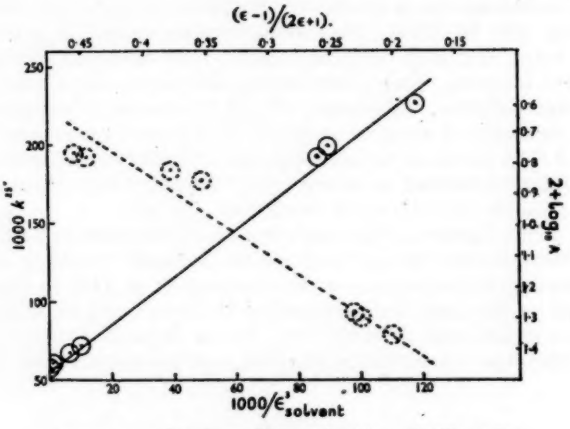
Oxime.	M_1.	Mean αE_2.	Mean β.	$_\infty P_1$.	$[R_L]_D$.	μ D.
m. p. 144°	165·15	1·66	0·345	88·4	39	$1{\cdot}5_5$
m. p. 112°	,,	1·99	0·272	102·2	,,	$1{\cdot}7_5$

With the benzaldoximes (Calderbank and Le Fèvre, *loc. cit.*) the more stable oxime has the lower m. p. and dipole moment. In the last-named respect, the piperonaldoxines are related in the opposite way. This is not in itself significant since (cf. this vol., p. 2374) the effect of the methylenedioxy-chain is to produce an additional vector acting with its negative pole towards the aromatic nucleus.

Isomerisation Rates of the Labile Piperonaldoxime.—With the data of Table I as a guide, it was obvious that density, rather than dielectric constant, would be the better rate-indicating property

for the present purpose. Since the actual evaluation of this as a function of time has no intrinsic relevance, *volume* changes have been observed instead. Dilatometers resembling those styled " Type C " in Fig. 1 of *J.*, 1938, 932 (Benford and Ingold), but of uniform bore throughout, were constructed from Pyrex capillary tube. They, with stoppered flasks holding predetermined quantities of the seven pure liquids of Table II, were immersed in thermostats set at 25° or 42·5°, the solute (weighed by difference) added to the solvent (this operation being taken as occurring at zero time in subsequent calculations), and the solution so formed sucked into the dilatometer *via* the inverted side arm. A scale (from a Beckmann thermometer) attached above the bulb allowed the expansion to be easily read with sufficient accuracy. The solvents were as specified in our previous paper (this vol., p. 944). Table II shows the first-order reaction constants found at each of the two temperatures together with frequency factors and energies of activation calculated therefrom.

FIG. 1.



– – – – – $2 + \log_{10} k^{25°}$ *against* $(\varepsilon - 1)/(2\varepsilon + 1)$.
——— $1000\ k^{25°}$ *against* $1000/\varepsilon^3$.

TABLE II.

Solvent.	k^{25} (hrs.$^{-1}$).	$k^{42·5}$ (hrs.$^{-1}$).	E (kcals./g.-mol.).	A (secs.$^{-1}$).
*cyclo*Hexanone	0·059	$0·71_7$	26·6	$5·9 \times 10^{15}$
Pyridine	0·061	$0·72_3$	26·3	$3·8 \times 10^{15}$
Chlorobenzene	0·068	0·78	$25·9_5$	$2·3 \times 10^{15}$
Chloroform	0·072	$0·80_6$	25·7	$1·4 \times 10^{15}$
Benzene	$0·193_5$	1·62	22·6	$2·5 \times 10^{13}$
Carbon tetrachloride	0·200	1·7	22·8	$3·4 \times 10^{13}$
*cyclo*Hexane	0·227	—	—	—

Discussion.—It is of interest first to compare our results with those of Patterson and McMillan (*loc. cit.*, 1908). These authors recorded first-order reaction constants between 20° and 30° in 2° steps, using ethyl tartrate as a solvent. Application of the Arrhenius equation to the various possible pairs of k_t gives, we find, a range of E values from 18 to 29 kcals./g.-mol. (the majority lying between 22 and 27 kcals./g.-mol.) and a related series for A from 10^{14} to 10^{17} sec.$^{-1}$. These figures are seen to be of an order comparable with those in Table II.

We will now compare the data of Table II with our observations (this vol., p. 944) on the *cis-* ⟶ *trans-p*-chlorobenzenediazocyanide inversions in the same media. Although the solvents do not affect both reactions in an identical manner the same general tendencies are seen.

Thus the velocities at 25° are :

for *p*-Cl·C_6H_4·N_2·CN : *cyclo*hexanone $< C_5H_5N < C_6H_6 < CCl_4 < CHCl_3 < C_6H_5Cl < C_6H_{12}$

for CH_2O_2:C_6H_3·CH:NOH : *cyclo*hexanone $< C_5H_5N < C_6H_5Cl < CHCl_3 < C_6H_6 < CCl_4 < C_6H_{12}$

The only significant difference is the position of chlorobenzene, since for the diazocyanide the magnitudes of k_{25} in benzene, carbon tetrachloride, and chloroform were similar.

The reaction is faster the lower the dielectric constant or the dipole moment appropriate to each solvent. Most of the correlations attempted previously (Le Fèvre and Northcott, *loc. cit.*)

for the diazo-compounds are slightly more satisfactory with this oxime, *e.g.*, plots of k against ε, $1/\varepsilon$, or $1/\varepsilon^{\frac{1}{2}}$, can be drawn to appear as imperfect *curves*; the plot of k against $1/\varepsilon^{\frac{1}{3}}$ shows more *rectilinearity* (see Fig. 1). Log k likewise varies with the dielectric constant of the solvent—its possible connection with $(\varepsilon - 1)/(2\varepsilon + 1)$ is included, as one example, in Fig. 1 (cf. Glasstone, Laidler, and Eyring, " The Theory of Rate Processes," McGraw-Hill, 1941, p. 420). Similarly,

FIG. 2.

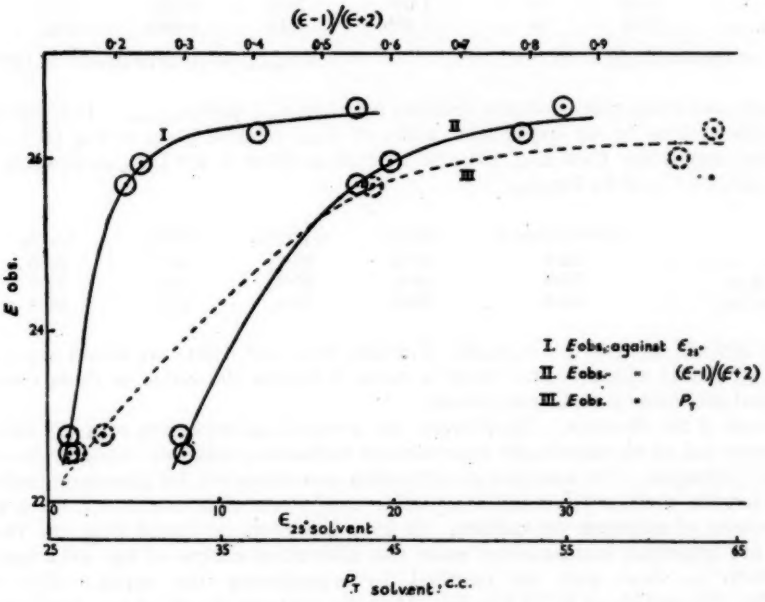
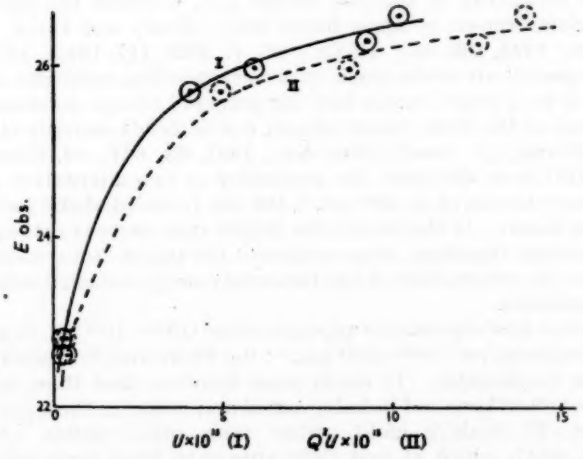


FIG. 3.



$E_{obs.}$ (from Table II) may be represented fairly smoothly against $\varepsilon_{solvent}$ or derivatives of it (see Fig. 2), or $\mu_{solvent}$, or U or Q^2U (see Fig. 3).

The last two quantities represent an attempt to estimate relative electrostatic interaction energies for different solvent–solute combinations; details and definitions are as already published (this vol., p. 944). The necessary data for Figs. 1—3 are in Table III, μ_{solute} being taken as 1·65 D. and r_{solute} as *ca.* 4·5 A.

With *p*-chlorobenzenediazocyanide the plots of $E_{obs.}$ against U (or Q^2U) approximated to

TABLE III.

	$\varepsilon^{25}_{solvent}$.	$\mu_{solvent}$, D.	$\alpha \times 10^{23}$, c.c.*	$r_{solvent}$, A.†	$\mu_M \times 10^{18}$.	$U \times 10^{15}$.	$Q^2U \times 10^{15}$.
*cyclo*Hexanone ...	18·2	2·8	1·09	3·12	$2·8_8$	10·5	14·0
Pyridine	12·4	2·3	0·95	2·87	$2·3_8$	9·3	12·6
Chlorobenzene ...	5·61	1·6	1·22	3·10	$1·6_9$	6·0	7·8
Chloroform	4·72	1·0	0·84	2·87	$1·1_7$	4·1	5·0
Benzene	2·27	0	1·03	2·96	$0·08_2$	$0·3_3$	$0·3_8$
Carbon tetrachloride	2·23	0	1·04	3·05	0·080	$0·3_1$	$0·3_6$
*cyclo*Hexane	2·04	0	1·09	3·16	0·080	$0·2_6$	$0·3_1$

* $\alpha = 0·0394\ [R_L]_D \times 10^{-23}$ c.c. † $r_{solvent} = (0·2916\ M/d)^{\frac{1}{3}} \times 10^{-8}$ cm.

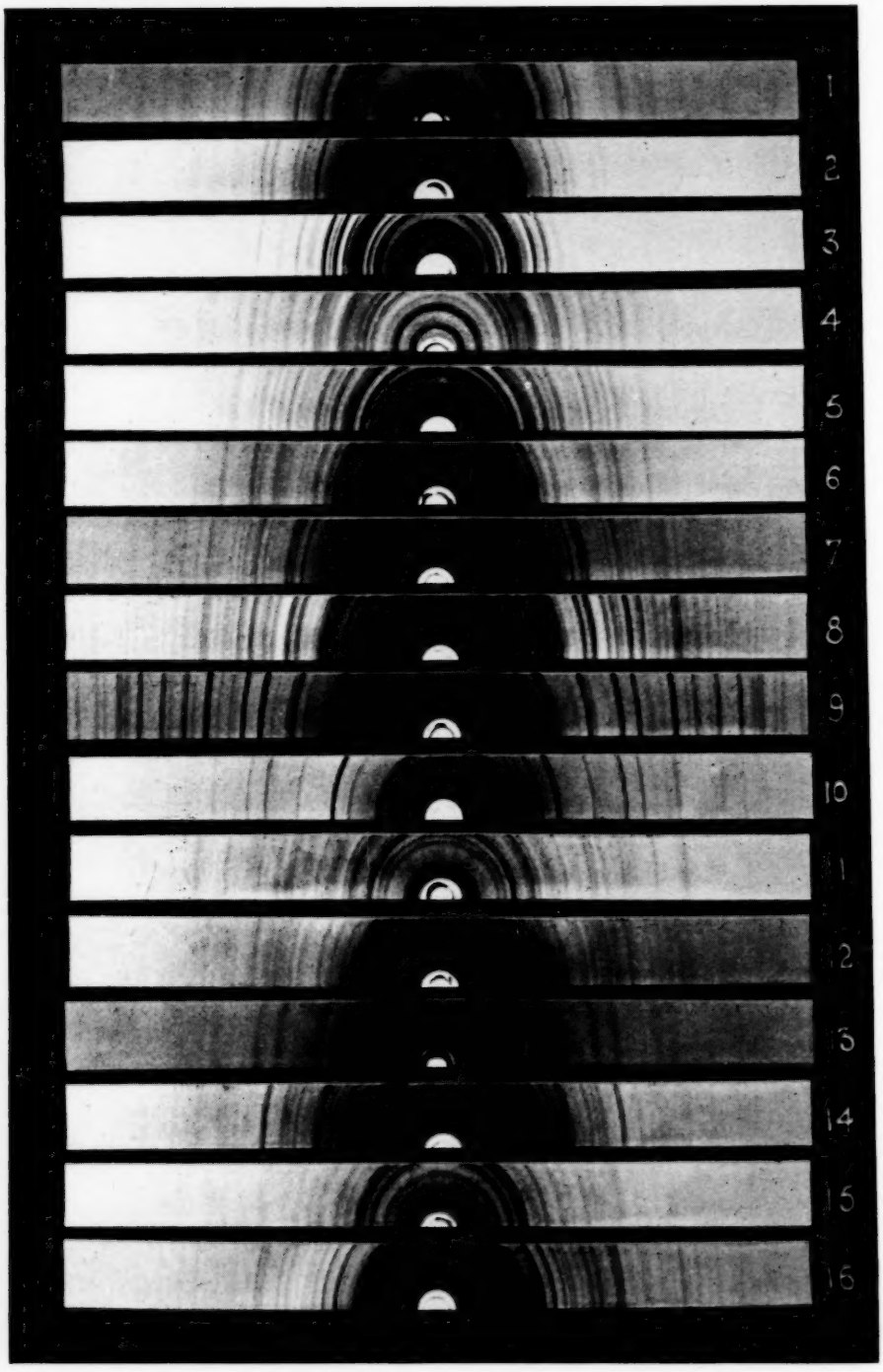
straight lines, and there was no direct relation between $E_{obs.}$ and $\mu_{solvent}$. For piperonaldoxime the connection seems to be hyperbolic, plots of $E_{obs.}$ against log μ or log Q^2U showing fair rectilinearity, suggesting that $E_{obs.}$ may be written as $(25·4 + 2·7 \log_{10} \mu)$ kcals./g.-mol., or, if μ_M be used, as $(25·4 + 2·45 \log_{10}\mu_M)$:

	*cyclo*Hexanone.	C_5H_5N.	C_6H_5Cl.	$CHCl_3$.	C_6H_6.	CCl_4.
$E_{obs.}$	26·6	26·3	$25·9_5$	25·7	22·6	22·8
$E_{calc.}$ (using μ)	26·6	26·4	$25·9_5$	25·4	22·7	22·7
$E_{calc.}$ (using μ_M)	26·5	26·3	$25·9_6$	25·6	22·7	22·7

Since ethyl tartrate has $\mu = 3·1$ D. at 25° (Faraday Soc. List, 1934), we would expect $E_{obs.}$ to be $26·7_3$ kcals./g.-mol in this solvent. Such a value is within the range of those calculable from Patterson and McMillan's data (see above).

Mechanism of the Reaction.—Intuitively the geometrical inversion of a >C=N− grouping might be expected to be kinetically intermediate between analogous changes about >C=C< and −N=N− linkages. The energies of activation now observed for piperonaldoxime resemble those obtained for *p*-chlorobenzenediazocyanide and, where E is concerned, show no effects of the replacement of nitrogen by carbon. It can, however, be urged that the instances just mentioned are improper comparisons, since the activating effects of the attached groups are ignored. Such a view may be justified by considering the series: Ph—N=N—Ph, Ph—CH=N—Ph and Ph—CH=CH—Ph. Here the first and the third member exist in isomeric forms which are interconvertible, whilst the second has so far been found only as the *trans*-structure (de Gaouck and Le Fèvre, *J.*, 1938, 741; 1939, 1392). Yet even among the oximes themselves a similar variability of stability occurs (*e.g.*, compare the piperonaldoximes with certain other aryl oximes known in single forms only; Brady and Dunn, *J.*, 1914, **105**, 821, 2409; 1915, **107**, 1858; 1916, **109**, 667; Brady *et al.*, *J.*, 1920, **117**, 1045; 1925, **127**, 2427; 1927, 894). Since azo-compounds are isoelectronic with corresponding molecules containing >C=N− and >C=C< there is no *a priori* reason why the potential energy–torsional rotation relations for analogous members of the three classes should not be fundamentally similar. For olefins, Magee, Shand, and Eyring (*J. Amer. Chem. Soc.*, 1941, **63**, 667; cf. Glasstone, Laidler, and Eyring, *op. cit.*, p. 324) have discussed the possibility of two alternative reaction paths, one adiabatic with frequency factors of *ca.* 10^{13} sec.$^{-1}$, the other non-adiabatic for which this quantity is many powers of ten lower. In the former the singlet state persists throughout; in the latter there is, through electronic transition, intervention of the triplet state, which for ethylene may be considerably below the intersection of the potential energy–torsional rotation curves for the *cis*- and *trans*-configurations.

The frequency factors now reported for piperaldoximé (10^{13}—10^{15} sec.$^{-1}$) and those previously noted for various azo-derivatives (10^{12}—10^{15} sec.$^{-1}$; Le Fèvre and Northcott, *loc. cit.*) in no way suggest non-adiabatic mechanisms. It would seem therefore that these isomerisations are to be compared with those of stilbene and its halogenated derivatives in the liquid phase ($A = 10^{10}$—10^{11} sec.$^{-1}$; $E = 34$—37 kcals./g.-mol.) rather than other olefins ($A = 10^{4}$—10^{5} sec.$^{-1}$, $E = 16$—27 kcals./g.-mol.), which at first sight appear to have more parallel energy factors (cf. Le Fèvre and Northcott, *loc. cit.*, for references). Our reactions may be examples where resonance in the activated state so lowers the intersection point (cf. above) that paths *via* triplet states never have an advantage (Magee, Shand, and Eyring, *loc. cit.*). The different E values for −CH=CH− and −N=N− systems could be understood if the resonance energies of members of the latter class were significantly greater than those of the former. Coates and Sutton (*J.*, 1948, 1187) have recently considered the energy excesses between the "normal" (*i.e.*, with central double bond) and possible activated (*i.e.*, with central single bond) structures of



Key to Plate.

X-Ray powder diagrams of :

(1) $Al_2(SO_4)_3,16H_2O$, *alunogen from Chile.*
(2) $Al_2O_3,2SO_3,11H_2O$.
(3) $5Al_2O_3,6SO_3,46H_2O$.
(4) $5Al_2O_3,6SO_3,40H_2O$.
(5) $Al_2O_3,SO_3,9H_2O$ (*aluminite*).
(6) $Al_2O_3,SO_3,6{\cdot}78H_2O$.
(7) $Al_2O_3,SO_3,5H_2O$.
(8) $Al_2O_3,SO_3,4H_2O$.
(9) *Australian alunite.*
(10) *Synthetic ammonium alunite* (1 *of Table IIA*).
(11) $2Al_2O_3,SO_3,xH_2O$ (*basaluminite*).
(12) $5Al_2O_3,3SO_3,xH_2O$.
(13) $11Al_2O_3,6SO_3,xH_2O$.
(14) $13Al_2O_3,6SO_3,xH_2O$.
(15) *Basic double salt I.*
(16) *Basic double salt II.*

[*To face p.* 2239.

stilbene, azobenzene, and benzylideneaniline. They argue (cf. formulæ, *loc. cit.*, p. 1192) that the order of resonance energies should be Ph—N=N—Ph > Ph—CH=N—Ph > Ph—CH=CH—Ph. Qualitatively therefore, that $E_{azobenzene}$ is *less* than $E_{stilbene}$ can be understood *a priori*, although why the intermediate anil has not yet been isolated in separate forms remains unclear.

On the same basis the action of polar solvents (on the oxime and various azo-derivatives) in slowing the inversion reaction *and* raising its energy of activation can be roughly ascribed to a diminution of resonance in the solute. Each solvent molecule, by direct electrostatic-field effects, will first cause induced moments in the polarisable solute and then tend to associate with it. A dissymmetrical electrical environment being thus produced, it is plausible that a *diminution* of electron mobility (reversible conjugation), and therefore of resonance energy, should result. This is equivalent to saying that the intersection point (see above) has moved away from the line representing the ground state.

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480. *The Basic Aluminium Sulphates.*

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The present investigation has followed more or less conventional phase-rule methods so far as the less basic compounds are concerned. The more basic compounds are so insoluble that their study had to depend much more upon finding satisfactory methods by which they could be prepared. Having found such methods it has been possible to examine their mutual relations and to determine, at least qualitatively, their regions of existence in the phase-rule diagram of the system Al_2O_3–SO_3–H_2O.

So far as the three-component system is concerned, the stable fields of existence of the more basic compounds are crowded into a very small space in the neighbourhood of the water point. It is clear that complex ionic, molecular, and micellar equilibria exist involving the numerous basic sulphates. The positions of these equilibria can be altered by change of temperature and are then readjusted only slowly, so that solutions can be obtained which have the same composition but yield different compounds. The system contains a great variety of phases. There are, besides $Al_2(SO_4)_3,16H_2O$, at least eight well-defined crystalline basic sulphates, most of which occur in more than one state of hydration.

In addition to these crystalline compounds, there are two quite different sets of two-liquid systems. Both of these form rough ellipses when plotted in an isothermal of the Al_2O_3–SO_3–H_2O system. Two-liquid system I is found in a relatively weakly basic region of the three-component system, and the second liquid phase occurs in the form of glassy discs or spheres.

Two-liquid system II occurs in the very basic region of the three-component system. Its second liquid phase constitutes the so called " hydroxide " precipitates obtained from sulphate solutions with ammonia and the gels thrown down from hydroxide sols with sulphate ions. The recognition of the liquid nature of " hydroxide precipitates " appears to be of some importance.

Two well-defined and well-crystallised basic double salts have been obtained. These are $(NH_4)_2SO_4,[11Al_2O_3,6SO_3,xH_2O]$ and $6(NH_4)_2SO_4,[11Al_2O_3,6SO_3,xH_2O]$. The " alunites," another group of basic double salts, are also important in connection with the system Al_2O_3–SO_3–H_2O. These compounds are usually given the formula $M^I[Al_3(OH)_6](SO_4)_2$, but such varied types of substitution are possible in the crystal lattice that the composition can differ greatly from that required by the conventional formula. Alunites can exist which contain only Al_2O_3, SO_3, and H_2O.

The *X*-ray diagrams of all the compounds obtained during the investigation have been examined, as have those of a number of minerals reputed to be basic aluminium sulphates. The only basic aluminium sulphate minerals (other than the alunites) which are really well-defined compounds are " aluminite " $Al_2O_3,SO_3,9H_2O$, and a new mineral $2Al_2O_3,SO_3,xH_2O$, which occurs in two different stages of hydration (Bannister and Hollingworth, *Nature*, 1948, **162**, 565). The less hydrated form with x about 10 has been called " basaluminite "; the other, with x of the order of 30, has been distinguished by the name " hydrobasaluminite." These three minerals have perfectly distinct and characteristic *X*-ray spectra but, for some reason, all our efforts to prepare them synthetically have failed. Two of the other supposed basic aluminium sulphate minerals examined by us gave " alunite " *X*-ray diagrams. All these minerals appear to need re-examination. The *X*-ray diagrams of aluminium sulphate and of all the basic sulphates dealt with in this paper are shown on the plate. Measurements of the spacings and intensities of their lines are recorded in the appendix.

Compounds discussed in this paper.

Formula.	Compn. of solid, %- Al_2O_3.	SO_3.	Referred to as :	No. of *X*-ray diagram on the plate.
$Al_2O_3,3SO_3,16H_2O$ $[Al_2(SO_4)_3,16H_2O]$	16·19	38·10	Aluminium sulphate	(1)
$Al_2O_3,2SO_3,11H_2O$ [possibly $[Al(OH)(H_2O)_5][SO_4]$	22·18	34·79	—	(2)
*$5Al_2O_3,6SO_3,46H_2O$	28·05	26·40	—	(3)
*$5Al_2O_3,6SO_3,40H_2O$	29·83	28·07	—	(4)
$Al_2O_3,SO_3,9H_2O$	29·65	23·26	Aluminite	(5)
*$5Al_2O_3,6SO_3,36H_2O$	31·14	29·30	—	(6)
*Al_2O_3,SO_3,xH_2O (x = *ca.* 6·78)	33·56	26·31		
*$Al_2O_3,SO_3,5H_2O$	37·50	29·42	—	(7)
*$Al_2O_3,SO_3,4H_2O$	40·16	31·42	—	(8)
A very wide range of solid solutions (see text) derived from the original compound $K[Al_3(OH)_6][SO_4]_2$	—	—	The alunites	(9)
	—	—	—	(10)
An aqueous and a glassy phase in equilibrium	—	—	Two-liquid system I	—
An aqueous and an amorphous phase in equilibrium	—	—	Two-liquid system II	—
$2Al_2O_3,SO_3,xH_2O$ (x = perhaps 30)	—	—	Hydrobasaluminite	—
$2Al_2O_3,SO_3,yH_2O$ (y = *ca.* 10)	43·96	17·25	Basaluminite	(11)
*$5Al_2O_3,3SO_3,xH_2O$ (x ,, 32)	38·47	18·10	—	(12)
*$7Al_2O_3,3SO_3,xH_2O$ (x ,, 33)	46·13	15·51	—	—
*$11Al_2O_3,6SO_3,xH_2O$ (x ,, 66)	40·22	17·20	—	(13)
*$13Al_2O_3,6SO_3,xH_2O$ (x ,, 83)	40·13	14·54	—	(14)
*$(NH_4)_2SO_4,[11Al_2O_3,6SO_3,xH_2O]$ (x = *ca.* 66)	38·40	19·17	Basic double salt I	(15)
*$6(NH_4)_2SO_4,[11Al_2O_3,6SO_3,xH_2O]$ (x = *ca.* 72)	30·41	26·02	Basic double salt II	(16)
α-$Al_2O_3,3H_2O$	—	—	Bayerite	—
γ-$Al_2O_3,3H_2O$	—	—	Hydrargillite (gibbsite)	—
α-Al_2O_3,H_2O	—	—	Diaspore	—
γ-Al_2O_3,H_2O	—	—	Boehmite	—

* New compounds are denoted by asterisks.

THE introduction in 1936 of a solution of basic aluminium sulphate as a scrubbing agent for the removal of sulphur dioxide from smelter gases (I.C.I. Ltd., B.P. 445,711; Fr. Pat. 796,421) made a phase-rule study of the system Al_2O_3–SO_3–H_2O desirable. This was also needed for a proper understanding of the manufacture of aluminium sulphate and of the setting of cement containing added gypsum.

There are at least five methods by which basic aluminium sulphate solutions may be prepared. They are: (i) Removal of part of the SO_4 radical from aluminium sulphate solutions by means of calcium hydroxide or carbonate. (ii) Dissolution of aluminium hydroxide in solutions of sulphuric acid or aluminium sulphate. (iii) Action of sulphuric acid or aluminium sulphate solutions upon amalgamated aluminium. (iv) Action of sulphuric acid upon clay or shale. (v) Methods involving the intermediate formation of positive sols of aluminium hydroxide.

Method (i) is used technically in the I.C.I. sulphur dioxide recovery process, and methods (ii) and (iv) are used technically for the manufacture of aluminium sulphate; none is suitable for preparing the pure solutions required for an exact phase-rule investigation.

Method (ii) was used by the only previous investigators of the basic region of the system Al_2O_3–SO_3–H_2O (Kremann and Hüttinger, *Jahrb. Geol., Reichsanstalt, Wien*, 1908, **58**, 639; Wirth, *Z. anorg. Chem.*, 1913, **79**, 360). The interaction of the aluminium hydroxide and sulphate is slow and difficult, especially in the more dilute and basic solutions, so although the method enabled Kremann and Hüttinger to prepare the least basic of the basic aluminium sulphates and to determine its solubility curve, it did not give correct indications otherwise (but see p. 2249).

Method (iii) was devised by Mr. A. M. Clark at Billingham, who also carried out a preliminary phase-rule study of the Al_2O_3–SO_3–H_2O system. All his results were available and were of great assistance in starting the fuller survey. This method was employed for preparing practically all the mixtures used in the solubility work to be described. It is easy of application, and mixtures of any desired composition can be prepared over a wide range of composition. It has its limitations, however, and pure crystalline basic aluminium sulphates with an Al_2O_3/SO_3 ratio greater than 1 cannot, as a rule, be prepared by this method (but see p. 2260). The very basic compounds are best prepared by method (v), which has been described by Bassett and Durrant (*J.*, 1942, 277). The ratio Al_2O_3/SO_3 is referred to as R in the following pages.

Preparation of Mixtures for the Phase-rule Work by Method (iii).—It was found better to use sulphuric acid rather than aluminium sulphate since even the " AnalaR " quality of the latter contained traces of ammonium which caused trouble. The requisite amounts of pure aluminium, sulphuric acid of suitable concentration, and water, weighed to the nearest deci- or even centi-gram, together with a small amount of metallic mercury, were placed in a beaker, usually of silica, and counterpoised, so that at the end of the reaction water lost by evaporation could be replaced or, alternatively, more could be driven off. Reaction was started by warming, and when all the aluminium had dissolved the solution was decanted from globules of mercury and filtered on the pump, through asbestos, from a small amount of black, finely dispersed, mercury containing traces of iron. The filtered solutions were either allowed to deposit solid spontaneously or were suitably inoculated with previously obtained solid phase. The mixtures should be prepared of such compositions that solid phase does not start to separate before it has been possible to filter the solutions. This limits the proportion of solid to liquid phase which can be obtained for any one mixture especially in the more basic region. Heating the more basic solutions is liable to cause separation of solid and, when these are being prepared, dissolution of the aluminium should be started by heating and then allowed to proceed to completion without further application of heat.

Time required for Establishment of Equilibrium between Solid Phase and Solution.—Supersaturated solutions of the basic salts may persist for long periods in absence of suitable nuclei. Once the latter have appeared, or been introduced, separation of solid occurs at a rate, roughly proportional to the amount of solid present, which is hastened considerably by shaking. Four months were sometimes needed for the attainment of equilibrium, especially with the more basic mixtures, though a fortnight sufficed with the more acidic ones. Good crystals suitable for single crystal *X*-ray work were obtainable with difficulty and only from solutions allowed to crystallise slowly without stirring. All of the compounds are, however, well crystallised on a microscopic scale.

Methods of Analysis.—The comparatively rapid volumetric method (Craig, *J. Soc. Chem. Ind.*, 1911, **30**, 184), involving titration with standard sodium hydroxide with and without addition of potassium fluoride, which is suitable for purposes of plant control, was found not to be accurate or reliable enough for the present work. Gravimetric methods had to be employed.

It is usually stated in text-books (see, *e.g.*, Vogel, " Quantitative Inorganic Analysis," 1939, 479) that the direct precipitation of sulphate in the presence of aluminium is unsatisfactory and gives low results owing to adsorption of aluminium sulphate by the barium sulphate. On ignition the weight of Al_2O_3 formed from such aluminium sulphate is far less than that of the extra amount of $BaSO_4$ which would have been obtained had no adsorption of aluminium sulphate occurred. Previous separation of the aluminium as hydroxide after double precipitation is advised.

We find, however, that the presence of aluminium does not affect the results if the barium sulphate is precipitated from sufficiently dilute solutions which are not less than 0·2N with respect to free hydrochloric acid. The barium sulphate should, of course, be precipitated slowly with stirring from nearly boiling solutions, and the mixture digested for some hours, and left to cool and stand over-night before filtration. Excellent results are obtained by this procedure, which is not only less troublesome than that involving previous separation of the aluminium, but is also more accurate for, even after a second precipitation, the aluminium hydroxide still retains an appreciable amount of sulphate. The following experiments illustrate the correctness of the above statements.

Five determinations were made of the weight of barium sulphate obtained from 25·06 c.c. of 0·1094N-sulphuric acid. Precipitation as above, using 10 c.c. of approx. N-barium chloride, gave weights of barium sulphate as follows: (i) 10 C.c. approx. 2N-hydrochloric acid, 65 c.c. water: 0·3204 g. (ii) As in (i) but with the addition of 0·35 g. of $AlCl_3,6H_2O$: 0·3201 g. (iii) As in (i) but with 0·036 g. of aluminium dissolved in the hydrochloric acid: 0·3199 g. (iv) As in (i), but 0·19 g. of aluminium dissolved in 20 c.c. of the approx. 2N-acid was added and only 55 c.c. of water: 0·3203 g. (v) Without hydrochloric acid but with 75 c.c. of water: 0·3199 g. The proportion of aluminium to sulphate in (iii) was rather higher than that in $Al_2(SO_4)_3$, while in (iv) it was rather more than that in our most basic compound $7Al_2O_3,3SO_3,xH_2O$.

The average of the five determinations would make the normality of the sulphuric acid 0·1094. By standardisation against $K_2O,5B_2O_3,8H_2O$, the normality was 0·1093. In order to see what variations might be expected in a series of determinations carried out under as nearly as possible identical conditions, four successive lots of 25·06 c.c. of the standard sulphuric acid were withdrawn, and each was diluted to 100 c.c. and precipitated just below the boiling point by means of 10 c.c. of approx. N-barium chloride solution. After precipitation, the mixtures were digested for 3 hours over small flames and then left overnight before filtration. The weights of $BaSO_4$ obtained were 0·3194, 0·3198, 0·3201, 0·3197 g. The average of these weights would make the sulphuric acid 0·10935N.

The variation in the weights of barium sulphate obtained from these sulphuric acid solutions is of the same order as that found in the previous series in which aluminium was also present.

A curious feature of barium sulphate precipitates was noticed to which no previous reference has been found. Small amounts seem to be particularly liable to pass over the tops of filter papers and down the groove of the fold, and this occurs even when the precipitate is quite coarse, as after long-continued digestion of the precipitated mixture. This is not a question of passage *through* the filter paper or of subsequent separation from solution in the filtrate. The only way to avoid it seems to be by taking great care (i) to fit the filter paper very carefully, (ii) to keep the precipitate as near the apex of the filter-paper cone as possible, (iii) not to stir the precipitate on the paper during the washing, and (iv) to wash the rim of the filter paper with great care by letting drops of wash-water fall vertically on to it.

If the filtration and washing are carried out without special precautions, and filtrate and washings are stirred round gently with a glass rod, a small sediment of barium sulphate will be found to collect on the centre of the bottom of the beaker which may amount to 0·0002 g. or, in extreme cases, to 0·001 g.

The following results are instructive and were obtained during a further check of the analytical

methods. The material analysed was the " normal " aluminium sulphate which had been prepared by method (iii) (see p. 2240) and washed with absolute alcohol till quite free from acid and then air-dried. The Al_2O_3 content was 15·96% [Calc. for $Al_2(SO_4)_3.16H_2O$: 16·19%]. A series of determinations of the SO_3 content was made upon approx. 0·3 g. of the solid in each case. Other conditions are stated below. The percentage of SO_3 calculated for $Al_2(SO_4)_3.16H_2O$ is 38·10.

Vol. of 2N-HCl used, c.c.	0	3	6	5	3	10	20	20
Total vol. before addition of $BaCl_2$, c.c.	100	30	30	50	100	100	100	100
Vol. of approx. N-$BaCl_2$ used, c.c.	10	5	5	5	10	5	10	10
SO_3, %, in solid	37·30	37·41	37·21	37·41	37·41	37·53	37·55	37·56

In the last experiment in the above table the mixture after precipitation was digested for 16 hours over a small flame and then left to cool for 2½ hours before filtration. The precipitate could be seen with a pocket lens to be quite coarsely crystalline. In other cases the precipitated mixtures had been left overnight at room temperature, and the precipitates were finer.

In a final experiment using 0·3008 g. of the same aluminium sulphate, the aluminium was precipitated with a small excess of ammonia, the aluminium hydroxide was given several washes, rinsed from the paper, dissolved by digestion with 2 c.c. of concentrated hydrochloric acid, and reprecipitated with ammonia. The second precipitate was washed with 40 c.c. of solution containing 0·8 g. of ammonium chloride. Any sulphate still retained by the alumina was recovered by dissolving the hydroxide with 2 c.c. of concentrated hydrochloric acid, evaporating nearly to dryness, diluting to 50 c.c. and adding 2·5 c.c. of N-barium chloride. 20 C.c. of 2N-hydrochloric acid were added to the aluminium-free filtrates and the mixture precipitated hot with 10 c.c. of N-barium chloride and digested overnight over a small flame. The filtrate from the coarsely crystalline barium sulphate was evaporated to dryness, and the ammonium chloride volatilised; water was added to the residue and an appreciable amount of barium sulphate was recovered which had been kept in solution by the hydrochloric acid and ammonium salts.

The details are:

First wt. of $BaSO_4$ from aluminium-free filtrates (this would correspond to only 37·25% SO_3 in the aluminium sulphate)	0·3268 g.
$BaSO_4$ from sulphate still retained by the aluminium hydroxide	0·0011 g.
$BaSO_4$ obtained after evaporation of filtrate from main lot of $BaSO_4$ and volatilisation of NH_4Cl	0·0022 g.
Deduct for ash of filter papers	0·0003 g.
Total wt. of $BaSO_4$	0·3298 g.

This corresponds to 37·60% of SO_3 in the aluminium sulphate.

The above experiments show that perfectly satisfactory sulphate determinations can be made in presence of large amounts of aluminium salts if a weight of barium sulphate of the order of 0·3 g. is precipitated from a volume of solution of about 100 c.c. containing 10 c.c. of 2N-hydrochloric acid as free acid, using not less than 5 c.c. of N-barium chloride as precipitant (cf. Shu-Chuan Liang and Tze-Wen Ann, *J. Chinese Chem. Soc.*, 1946, **14**, 17; *Brit. Abs. C*, 1948, 4). The figures Al_2O_3, 15·96%; SO_3, 37·60% give $R = 0·333$, which is correct for $Al_2(SO_4)_3$. Aluminium was always determined on a separate portion if possible. It was precipitated in presence of methyl-red with a very small excess of ammonia and the mixture boiled till neutral to the indicator. Thorough washing of the precipitate was not necessary when aluminium was the only non-volatile constituent present, and this saved much time. When thorough washing was needed, as in analyses of alunogen or other minerals, it was essential to do the later part of the washing with a 2% solution of ammonium chloride or nitrate, otherwise serious errors could occur owing to aluminium hydroxide becoming peptised and passing through the filter-paper. The aluminium hydroxide and filter-paper were ignited first over the Bunsen burner until all carbon had been removed and then for an hour in an electric muffle at about 1200°. This ignition at a high temperature is needed for two reasons: (i) to convert the γ-Al_2O_3 into the non-hygroscopic α-Al_2O_3 or corundum form, and (ii) to decompose the last traces of sulphate.

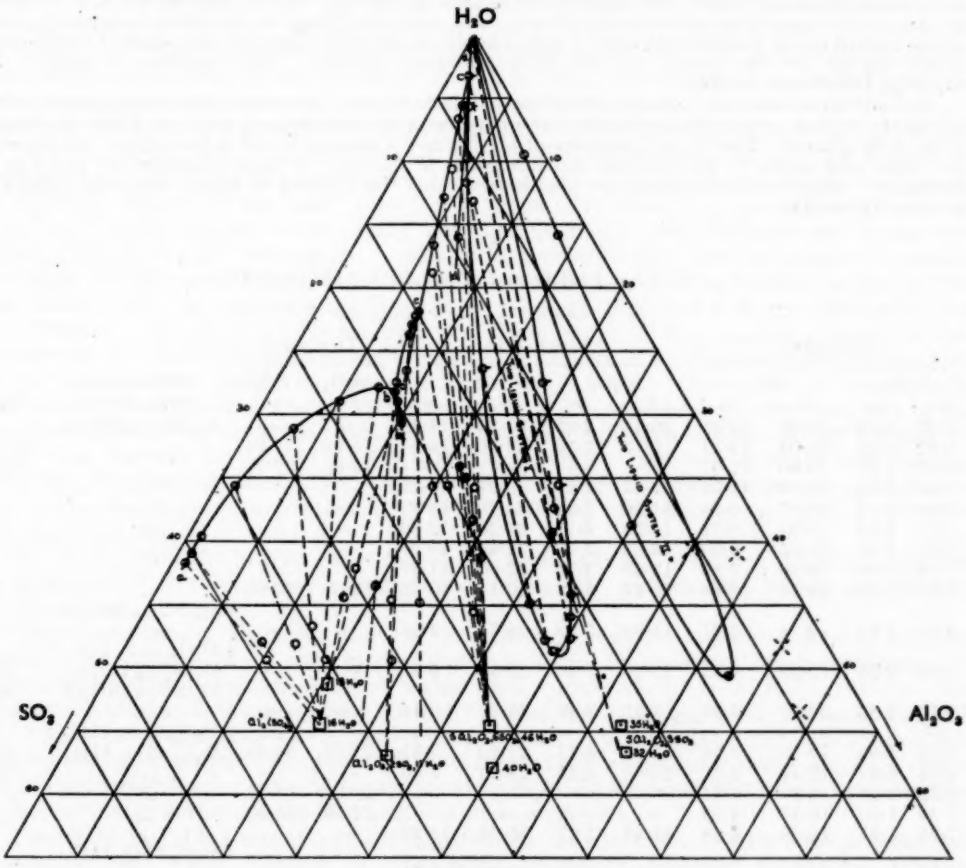
If the alumina remains in the γ-condition it increases in weight so quickly that, even with very rapid weighing, it is difficult to be sure of the correct weight. Quite important errors can be caused by the presence of undecomposed sulphate if the temperature of ignition has not been greater than 800° or 900°. In certain cases owing to shortage of material the sulphate and alumina estimations had to be made on the same sample. It was then essential to precipitate the sulphate first, as above, remove excess of barium as sulphate, and finally precipitate the alumina. If the analysis is done the other way round low results for sulphate are obtained, even after double precipitation of the alumina, as can be seen from the analysis quoted above.

Treatment of Mixtures before Analysis.—The mixtures were placed in either silica or glass tubes closed by waxed corks, the upper part of the tube and the cork being well covered by wax. After the tubes had been shaken at 25° for a sufficient time, solid and solution were separated for analysis through asbestos and a disc of hardened filter paper in a jacketed filter-tube. Solution and " moist solid " were analysed, and in many cases " dry solid " also. The last was obtained from " moist solid " by washing either with water or with alcohol of increasing concentration, and drying at room temperature. Water alone is the best initial wash-liquor for all the basic salts, except the least basic one ($Al_2O_3.2SO_3.11H_2O$) or for $Al_2(SO_4)_3.16H_2O$ which dissolve in cold water, but the minimum amount should be used. In some cases addition of water to the mother-liquor causes a precipitate to form, and in such cases, after removal of the mother-liquor as completely as possible, the wash-water must be added in very small amounts, with the pump full on, so as to ensure that dilution is gradual and that the diluted liquor is

removed before it can deposit any precipitate. When alcohol washing is used the alcohol must be diluted with sufficient water to prevent formation of a precipitate on addition to small amounts of the mother-liquor. The washing is continued with progressively more concentrated alcohol.

All solid phases were examined with the polarising microscope, and *X*-ray powder photographs were taken of all dry solids. The compositions of equilibrium solutions and of the corresponding moist and/or dry solid phases are given in Tables I—VII and shown graphically in Fig. 1. In Tables I and II the compositions of solutions and moist solids are given both as weight and as molecular percentages Molecular percentages are, of course, most suitable if comparisons are to be made with other systems.

FIG. 1.



Key to Fig. 1.

System Al_2O_3–SO_3–H_2O *at* 25°.

Solubility curves of :

$Al_2(SO_4)_3,16H_2O$	*a b a*
$Al_2O_3,2SO_3,11H_2O$	*b c*
$5Al_2O_3,6SO_3,46H_2O$	*c c c*
$5Al_2O_3,3SO_3,xH_2O$	*d c d*

Two-liquid system I

Two-liquid system II

Points given by hydroxide sol curds

They do, however, suffer from the disadvantage that, owing to the small molecular weight of " H_2O," the results for a system such as the present one are unduly crowded up towards the H_2O apex when plotted in a triangular diagram. Weight percentages have been used, for this reason, in plotting Fig. 1.

In the case of solid phases containing combined water it is important to know that the separated dry solid contains the same amount of water as it did when in equilibrium with the saturated solution. In a number of cases the separated solid phases were equilibrated as follows. A light glass bucket containing a weighed amount (0·1—0·2 g.) of air-dried solid phase was suspended above some of the equilibrium solution, contained in a wide glass tube of about 25 c.c. capacity. The bucket was hung on a platinum hook fixed into the waxed cork closing the tube. The upper part of the tube and the cork were thoroughly waxed over and the tube was then placed in a suitable rack and immersed in the thermostat at 25°. The tube was periodically opened after known time intervals and the bucket

transferred to a weighing bottle and weighed. By plotting the various weighings it could easily be seen how the approach to the final equilibrium weight was proceeding. This procedure was found to be very satisfactory and simpler and better than several others which were tried. The pressure of aqueous vapour given off by a hydrated salt is equal to or less than that of its equilibrium solution at a given temperature. If the partially dehydrated salt is exposed over some of the equilibrium solution at this temperature water vapour will be absorbed by the salt until the hydrate has been fully re-formed, the salt then ceasing to increase in weight. Further absorption of moisture will not normally occur in a three-component system, for, even if a slight irregularity of temperature causes momentary condensation on the solid, this cannot dissolve in the condensed moisture to give a solution of the same composition as the equilibrium solution unless the solid is congruent to the particular solution. In all other cases in three-component systems any moisture condensed in this way on the crystals tends to evaporate as soon as the temperature disturbance is over. The method will lead to somewhat high results for the water content of the equilibrated solid if this is finely divided and if there is any marked adsorption of water vapour by the surface of the fully hydrated material. This appears to happen with $Al_2(SO_4)_3,16H_2O$ (see p. 2245).

It would have been very difficult, if not impossible to unravel the complicated relationships existing among the various compounds dealt with in this paper without the assistance given by *X*-ray examination of all solid phases. The *X*-ray diagrams of all the new compounds and a few others are shown in the plate, and tables of the spacings and intensities of the lines in these diagrams are given in the appendix. Similar measurements are also recorded for the alunites of which analytical details are given in Table IIA.

TABLE I.

$Al_2(SO_4)_3,16H_2O$ *and* $Al_2O_3,2SO_3,11H_2O$ *at* 25°.

(*w* = weight %; *m* = molecular %.)

Solution.				Moist solid.				Dry solid.			
Al_2O_3.		SO_3.		Al_2O_3.		SO_3.		Al_2O_3.	SO_3.	Nature of	
w.	*m.*	*w.*	*m.*	*w.*	*m.*	*w.*	*m.*	*w.*	*w.*	solid phase.	Notes.
0·92	0·24	40·98	13·41	10·18	2·93	39·23	14·42	—	—	$Al_2(SO_4)_3,16H_2O$	
0·97	0·25	40·03	13·21	9·13	2·59	38·90	14·04	15·96	37·64	,,	(1), (2)
0·97	0·25	38·90	12·67	—	—	—	—	15·96	37·54	,,	(2)
1·39	0·34	34·39	10·72	11·53	3·28	36·61	13·26	—	—	,,	
3·09	0·72	28·07	8·34	11·96	3·34	34·79	12·39	—	—	,,	
5·20	1·19	23·93	6·98	14·20	4·11	35·22	12·99	—	—	,,	
7·36	1·66	20·55	5·93	13·05	3·55	31·45	10·91	—	—	,,	
7·74	1·75	20·20	5·83	13·49	3·71	32·06	11·27	—	—	,,	
7·71	1·74	20·14	5·80	12·47	3·32	30·14	10·22	16·07	37·82	,,	(1), (2)
8·56	1·94	19·71	5·71	14·80	3·98	28·74	9·86	—	—	$Al_2(SO_4)_3,16H_2O$ and $Al_2O_3,2SO_3,11H_2O$	
9·08	2·08	19·98	5·83	12·86	3·40	29·37	9·92	—	—	$Al_2(SO_4)_3,16H_2O$	(2)
10·15	2·36	20·50	6·09	13·51	3·46	25·82	8·44	—	—	$Al_2(SO_4)_3,16H_2O$ and $Al_2O_3,2SO_3,11H_2O$	(3)
8·62	1·95	19·55	5·66	15·61	4·17	27·30	9·31	22·22	34·95	$Al_2O_3,2SO_3,11H_2O$	(4)
8·48	1·92	19·44	5·61	16·45	4·49	28·15	9·80	—	—	,,	(5)
7·39	1·61	16·40	4·54	—	—	—	—	22·15	34·85	,,	(6)
7·34	1·60	16·35	4·53	—	—	—	—	22·15	34·80	,,	
7·25	1·57	15·90	4·38	18·86	5·47	30·54	11·30	—	—	,,	
7·16	1·53	15·11	4·12	18·52	5·08	26·40	9·24	—	—	$Al_2O_3,2SO_3,11H_2O$ and $5Al_2O_3,6SO_3,46H_2O$	

Notes to Table I.—(1) These two solid phases were shown to be identical by their *X*-ray powder photographs.

(2) Mixtures prepared by the amalgamated aluminium process; the other mixtures where the solid phase was only $Al_2(SO_4)_3,16H_2O$ had been prepared from " AnalaR " aluminium sulphate.

(3) This experiment gives a point on the metastable portion of the $Al_2(SO_4)_3,16H_2O$ curve. Microscopic examination showed that some crystals of $Al_2O_3,2SO_3,11H_2O$ were present in the solid phase which was, however, mostly $Al_2(SO_4)_3,16H_2O$. As more $Al_2O_3,2SO_3,11H_2O$ separated the composition of the solution would gradually approach the value 8·56% Al_2O_3; 19·71% SO_3.

(4) The solubility experiment with potassium alum (see p. 2246) was done with the solution from this experiment.

(5) Prepared as a residue from " AnalaR " $Al_2(SO_4)_3,16H_2O$ (see p. 2245).

(6) Particularly well-crystallised solid used for *X*-ray single-crystal work.

Consideration of the Compounds (i) $Al_2(SO_4)_3,16H_2O$ *and* (ii) $Al_2O_3,2SO_3,11H_2O$—(i) $Al_2(SO_4)_3,16H_2O$ (Plate I, Nos. 1 and 2). There still appears to be much uncertainty about the correct formula of ordinary aluminium sulphate. Most modern text-books and the " AnalaR " reagent labels call it $Al_2(SO_4)_3,18H_2O$ [some of the latest labels call it $Al_2(SO_4)_3$, aq.], although careful work by de la Charlonny (*Compt. rend.*, 1883, **96**, 844; 1890, **111**, 229;

Ann. Chim. Phys., 1884, **1**, 425) had shown that the hydration corresponded to 16 and not $18H_2O$. The reason for this uncertainty is to be sought in the characteristics of the compound. It is very soluble but extremely difficult to obtain in any but small, thin, fragile crystals. It is not easy to be sure that such crystals when analysed contain neither too much nor too little water. The present work has enabled the question to be settled by the method of residues in favour of the hydrate with only $16H_2O$. This method must be used with discretion, however. Motida published a paper on the system $Al_2(SO_4)_3$–H_2SO_4–H_2O (*Sci. Rep. Tôhoku*, 1938, **26**, 611) in which he stated that at 25° $Al_2(SO_4)_3,16H_2O$ was the stable hydrate in equilibrium with solutions containing from 41·5 to 21·6% of SO_3, but $Al_2(SO_4)_3,18H_2O$ was the solid phase over the range 21·4—19·7% SO_3. When his evidence is examined it is found to give no support to this statement. The analytical results are closely similar to those given in the present paper. The solution points all lie on one smooth curve with no sign of any break at the point suggested. At the strongly acid end of the curve the tie-lines run very near to the point for $Al_2(SO_4)_3,16H_2O$, but at the weakly acid end they run almost as well to the point for $Al_2(SO_4)_3,18H_2O$ as to that for $Al_2(SO_4)_3,16H_2O$, and so cannot make a clear distinction between them. This is because over the weakly acid range the tie-lines are inclined at only a very small angle to the line joining the $Al_2(SO_4)_3,16H_2O$ and the water point. The diagram in Motida's paper shows the one set of tie-lines running exactly to the point for $Al_2(SO_4)_3,16H_2O$ and the other set to that for $Al_2(SO_4)_3,18H_2O$, but this is found to be an unjustified simplification when his results are plotted on a large enough scale. There is no evidence in Motida's paper that he even looked at the solid phases under the microscope or that the supposed two different hydrates appeared in any way different. All the solid phases over the whole range of the $Al_2(SO_4)_3$ region in our experiments had the appearance of the crystals described by de la Charlonny (*loc. cit.*) and all the tie-lines run very closely to the point for $Al_2(SO_4)_3,16H_2O$. To make the identity still more certain, *X*-ray powder photographs were taken of one solid from the very acid end of the range and of one from the weakly acid end. They were indistinguishable. Lastly, it may be added that the dry crystals of $Al_2(SO_4)_3,16H_2O$ separated from the strongly acid solution (at 40·03% SO_3) had not changed in weight after exposure for 2 years at room temperature over some of the weaker solution (20·14% SO_3) which according to Motida should be in equilibrium with $Al_2(SO_4)_3,18H_2O$.

The latest claim (Smith, *J. Amer. Chem. Soc.*, 1942, **64**, 41), *viz.*, that $Al_2(SO_4)_3,17H_2O$ is the stable solid in equilibrium with saturated solution at 25°, can probably also be explained on the above lines.

It is of some interest, however, that the numerous preparations of pure aluminium sulphate obtained by filtration from acid mother-liquor followed by thorough alcohol-washing and air-drying invariably contained more water than corresponded to $Al_2(SO_4)_3,16H_2O$. The composition was generally very close to that required by $Al_2(SO_4)_3,16{\cdot}5H_2O$ (Al_2O_3, 15·96%; SO_3, 37·56%). This applies also to the very pure specimen of alunogen from Chile (see p. 2246). The phase-rule isothermal seems to make it certain that the compound is really $Al_2(SO_4)_3,16H_2O$ and it is probable that the extra half molecule of water in the air-dried solid is held by adsorption on the very large surface of the thin platy or fibrous crystals.

The results in Table I show that $Al_2(SO_4)_3,16H_2O$ is only just able to form a stable congruent solution at 25°. The solution at the point where it becomes metastable towards $Al_2O_3,2SO_3,11H_2O$ has an *R* value of only 0·3398 as compared with 0·333 for the congruent solution. " AnalaR " preparations of aluminium sulphate are often slightly basic and this is due to the presence of a small proportion of crystalline $Al_2O_3,2SO_3,11H_2O$.

51·9 G. of " AnalaR " sulphate were shaken at 25° with 48·1 c.c. of water which should just give 100 g. of saturated solution. After a very short time all but a very small amount of the solid had dissolved. This was allowed to settle and a little withdrawn for microscopic examination. It consisted of characteristic prisms of $Al_2O_3,2SO_3,11H_2O$. After further shaking for a fortnight the mixture was allowed to settle, and the bulk of the clear solution decanted. The rest was filtered for analysis and the figures recorded in Table I were obtained.

The weight of moist solid was 1·02 g., equivalent to 0·58 g. of dry $Al_2O_3,2SO_3,11H_2O$ from the position of the moist-solid point on the tie-line. This corresponds to 1·12% of $Al_2O_3,2SO_3,11H_2O$ in the " AnalaR " $Al_2(SO_4)_3,16H_2O$ or to slightly more if allowance is made for the small amount which had dissolved.

After 4 days at room temperature a number of small, bright, well-formed isotropic octahedral crystals had crystallised from the solution which had been decanted from the $Al_2O_3,2SO_3,11H_2O$. There was also present a little of the latter compound carried over during the original decantation. The actual amount of the octahedral crystals was very small, but most of it was obtained in a clean dry state by decantation, filtration, and washing with a little cold water followed by alcohol of increasing concentration. The weight of dry crystals finally obtained was only 0·0048 g., though little appeared to be lost in the separation. The crystals were identified as ammonium alum by the refractive index,

found to be 1·460 as compared with 1·4594 given in the International Critical Tables. This alum originates from the trace of ammonia (up to 0·02% according to the label) contained in " AnalaR " aluminium sulphate. The possibility of separating it in the manner described depends upon its enormously decreased solubility in the saturated aluminium sulphate solution as compared with pure water. This decreased solubility was studied with potassium alum at a time when it was thought that the octahedral crystals observed in several experiments might consist of potassium alum. The effect on the solubility of ammonium alum would be similar. 0·0181 G. of potassium chloride was shaken at 25° with 14·8 g. of the solution containing 8·62% Al_2O_3 and 19·55% SO_3 (see Table I) and after several days the potassium sulphate which had formed was dissolved by gentle heat. After 24 hours' further shaking the octahedral crystals of alum were filtered off and weighed on a sintered-glass Gooch crucible after being washed with alcohol of increasing concentration and air-drying. The weight was 0·0762 g. as compared with 0·115 g. theoretically obtainable. Since 100 g. of water at 25° can dissolve 14·14 g. of $KAl(SO_4)_2,12H_2O$ (Seidel, " Solubilities of Inorganic and Organic Substances," 1912, p. 13), the water present in the 14·8 g. of solution used in the experiment could have dissolved 1·502 g. of alum had it been pure water instead of the 0·0388 g. which it did dissolve.

The above experiments explained the very puzzling appearance in small amounts of isotropic octahedral crystals (or other cubic forms) from solutions in the immediate neighbourhood of the intersection of the solubility curves of $Al_2(SO_4)_3,16H_2O$ and $Al_2O_3,2SO_3,11H_2O$. For a long time it was thought that these must consist of some other basic aluminium sulphate or even of aluminium sulphate itself. They are not obtained when the solutions are prepared from aluminium and sulphuric acid. A similar separation of alum crystals probably explains a remarkable statement by Rammelsberg (" Handbuch der Krystallographischen Chemie," Berlin, 1855, p. 88) that $Al_2(SO_4)_3,18H_2O$ crystallised at the ordinary temperature in " regular(?) octahedra." He added : " It is, however, still doubtful whether the observed octahedra consist of the pure alkali free-salt."

$Al_2(SO_4)_3,16H_2O$ occurs naturally as the mineral " alunogen." We have shown that the *X*-ray spectrum of this mineral is identical with that of our $Al_2(SO_4)_3,16H_2O$. It is clear, therefore, that " alunogen " contains only 16 molecules of water and not the 18 assigned to it in most treatises on mineralogy. Under very dry conditions some of this water may be lost (Gordon, *Notulæ Naturæ, Acad. Nat. Sci. Philadelphia*, 1942, No. 101) as is, of course, liable to happen with most hydrated salts. Gordon gives it the correct formula.

We have taken the *X*-ray spectra of two specimens of alunogen : (1) the British Museum specimen B.M. No. 19911 from Rudnó, Nová Baňa, Pohronská Zupa, Slovakia, and (2) a specimen supplied by the Compagnie Minera Herminda, Santiago, Chile (the exact locality from which it came is not known to us). In all cases where we have been able to examine British Museum specimens it has been through the kindness of Dr. Max Hey of the British Museum (Natural History) Dept. of Mineralogy. He also supplied much helpful information about the minerals concerned and the individual museum specimens. The South American specimen is in the form of large white or slightly pink masses with a rather fibrous crystalline structure, and is remarkably pure. It contained only 0·2% of insoluble matter, chiefly angular quartz fragments and a little ferruginous material, and the water-soluble portion contained : Al_2O_3, 15·88; CuO, 0·04; MgO, 0·02; SO_3, 37·40%. No iron was present in the water-soluble material. After deduction of SO_3 equivalent to the CuO and MgO, *R* for the aluminium sulphate is 0·334.

The traces of magnesium and copper sulphates would account for 0·10% of the water present in the mineral if they are present as $MgSO_4,Al_2(SO_4)_3,22H_2O$ and $CuSO_4,Al_2(SO_4)_3,22H_2O$, which is most probable. This would leave, by difference, $46{\cdot}56H_2O$ for the aluminium sulphate. This would give a composition Al_2O_3, 15·92; SO_3, 37·40; H_2O, 46·68% for the pure compound. This is very close to the composition required by $Al_2(SO_4)_3,16{\cdot}5H_2O$, which is Al_2O_3, 15·96; SO_3, 37·56; H_2O, 46·49%.

(ii) $Al_2O_3,2SO_3,11H_2O$. The compound $Al_2O_3,2SO_3,11H_2O$ forms well-developed, though small, monoclinic prisms which are very stable in the air and do not pick up any water when exposed over their saturated solutions at 25°. The extinction angle is at about 16° to the length of the prism. The compound dissolves fairly quickly in cold water to give a clear solution, which soon becomes milky, but it cannot form a congruent solution. It is quite clear from our results that only 11 molecules of water are present and not 12.

Unexpected difficulties have been encountered in the interpretation of the crystal structure of $Al_2O_3,2SO_3,11H_2O$, but the *X*-ray data make it very probable that the ion $[Al(OH)(H_2O)_5]^{\cdot\cdot}$ is present and that the compound is to be regarded as the salt $[Al(OH)(H_2O)_5]SO_4$. We have also prepared the compound as follows during experiments to devise a satisfactory method for preparing the corresponding selenate. 2·25 G. of aluminium were dissolved in 112 c.c. of 2·053N-hydrochloric acid, helped by gentle heating, 30 hours being required for complete solution. 35·83 G. of silver sulphate (the calculated amount) were added to the clear boiling solution, and the mixture heated in a gently boiling water-bath

for several hours. The hard lumps of silver chloride were crushed, and the mixture left overnight, but as unaltered silver sulphate was then still present in the solid phase; the mixture was diluted to 200 c.c. and heated over a small flame for another 24 hours, by which time no unreacted silver sulphate remained. The clear filtrate from the silver chloride and washings was evaporated in a silica beaker until the weight was 48·3 g. This concentrated solution after inoculation with a few crystals of $Al_2O_3,2SO_3,11H_2O$ was shaken at 25° for 3 weeks; the solid phase was then filtered off, washed with alcohol of increasing concentration, and air-dried; yield 3·3 g. (Found: Al_2O_3, 22·03; SO_3, 34·60. Calc. for $Al_2O_3,2SO_3,11H_2O$: Al_2O_3, 22·18; SO_3, 34·79%).

The amounts employed in the above preparation were such as should give a solution containing 7·6% Al_2O_3; 17% SO_3, which lies on the 25° solubility curve of $Al_2O_3,2SO_3,11H_2O$, together with several g. of the solid.

Marguerite (de la Charlonny) (*Compt. rend.*, 1880, **90**, 1354) obtained this compound by controlled decomposition of ammonium alum to give a residue almost entirely soluble in water from which it crystallised in rhombohedra. He assigned to it the formula $Al_2O_3,2SO_3,12H_2O$. According to Mans (*Pogg. Ann.*, 1827, **11**, 80) it can be got by evaporation to dryness of a hot filtered solution of aluminium hydroxide in aluminium sulphate, and Spence [B.PP. 25683 (1902); 6458 (1903); Fr. Pat. 331836 (1903); German Pat. 167419 (1903); U.S. Pat. 754824 (1904)] made it by mixing a solution of aluminium sulphate with enough calcium hydroxide or carbonate to give the necessary basicity. The filtered solution was evaporated *in vacuo*, and the crystals obtained were separated by centrifuging. If evaporation is carried to dryness, a pure product would not be obtained by either method, since the compound does not form a congruent solution.

Kremann and Hüttinger (*loc. cit.*) determined the solubility curve of this compound at several temperatures. They accepted the formula $Al_2O_3,2SO_3,12H_2O$ and supposed that it corresponded to the mineral "alumian." This mineral has been under suspicion for some time. It was first described and named by Breithaupt (*Berg. u. Huttenmännische Z.*, 1858, **17**, 53) and was based upon a very incomplete and unsatisfactory analysis by Utendörffer who gave it the formula $Al_2O_3,2SO_3$. It is stated in Breithaupt's paper that the mineral contained 37 to 38% Al_2O_3 and "only hygroscopic water."

Hlawatsch (Festschr. V. Goldschmidt, Heidelberg, 1928, p. 162) suggested on incomplete evidence that "alumian" might be identical with "alunite," and Gordon (*Notulæ Naturæ, Acad. Nat. Sci. Philadelphia*, 1940, No. 57) considered that it was to be identified with "natro-alunite."

We have been able to determine the *X*-ray spectra of two specimens of "alumian" in the British Museum collection. The numbers of these specimens in the British Museum Catalogue are: (i) B.M. 35864 which, according to A. Krantz, Berlin, from whom it was purchased, came from Barranco Farosso, Sierra Almagrera, Granada, Spain; (ii) B.M. 92951, which came from Abelardo Mine, Barranco del Francis, Sierra Almagrera, Almeria, Spain. This was in the Allan Greg collection purchased by the Museum in 1860, came from the original locality and bears a label in Breithaupt's handwriting. It must, therefore, be regarded as "type material." The *X*-ray spectra of these two specimens proved to be almost identical with those of three specimens of "alunite" from our own collection. These were: (i) a very well-crystallised specimen from Muszaj, Komitat Beregh, Hungary; (ii) a massive, coarsely crystalline specimen from near Marysvale, Utah, United States; (iii) a similar specimen, from Bulladelah, near Newcastle, New South Wales, Australia. It seems certain, therefore, that the mineral called "alumian" by Breithaupt and given the formula $Al_2O_3,2SO_3$ was in fact "alunite." Its insolubility in water is in agreement with this. The existence of the anhydrous $Al_2O_3,2SO_3$ as a mineral is improbable in any case.

The Compound $5Al_2O_3,6SO_3,46H_2O$ (*Plate, No.* 3).—$Al_2O_3,2SO_3,11H_2O$ has a comparatively small range of existence. The next solid phase to appear at 25° on passing into less concentrated and more basic regions of the system is the compound $5Al_2O_3,6SO_3,46H_2O$. This is stable over the range Al_2O_3, 7·17; SO_3, 15·11 to Al_2O_3, 1·24; SO_3, 2·19%. The relevant data are given in Table II (p. 2250). The study of this compound was much more troublesome than that of $Al_2O_3,2SO_3,11H_2O$. In comparison with the latter it is only very sparingly soluble and comes into equilibrium with its solutions far more slowly. At the more dilute end of its range its solubility curve runs very close to the curve of two-liquid system I so that solutions prepared of suitable concentrations to yield reasonable amounts of the compound $5Al_2O_3,6SO_3,46H_2O$ start off by being supersaturated not only to this but also to the glassy solid of the two-liquid system. The latter separates more readily than the former and may become occluded in the crystals of $5Al_2O_3,6SO_3,46H_2O$ when these do eventually separate. All the solution–moist solid tie lines for this part of the diagram run very close indeed to the point for $5Al_2O_3,6SO_3,46H_2O$

(Calc. : Al_2O_3, 28·05; SO_3, 26·40%), so there can be little doubt that the crystals in equilibrium with the solutions have this composition. At one time it was thought that they represented a series of solid solutions, though the fact that the *X*-ray diagrams were identical over the whole range was rather against this view. Many of the solids were separated from their mother-liquors by filtration and washing with either water or a mixture of alcohol and water followed by air-drying. They were then analysed either in the air-dry condition or after equilibration over the mother-liquors. This was to obtain evidence for or against the possibility that the crystals consisted not of a definite compound but of a series of solid solutions. A difficulty in the method lies in the possibility that the composition of the solid phase may be altered during its separation from the liquid. The danger of this in the present case did not seem serious since the crystals are relatively insoluble in water. Two experiments were made to test the point with a preparation to which Note 3 of Table II refers.

(*a*) 1 G. of the preparation was slowly washed on an ordinary filter-paper and funnel with 50 c.c. of distilled water. The washings became slightly milky almost as soon as they had run through, and a small amount of the " glassy solid " phase of the two-liquid system I slowly settled out. The composition of the washed and air-dried solid remaining in the funnel was Al_2O_3, 28·00; SO_3, 26·16%; $R = 0·84$. The *X*-ray diagram of the washed solid was still that of $5Al_2O_3,6SO_3,46H_2O$.

(*b*) 3 G. of the same preparation were washed on a filter-paper and ordinary funnel with 600 c.c. of distilled water for about a week. After air-drying, the solid residue, now 1·79 g., contained Al_2O_3, 32·26; SO_3, 21·09%; $R = 1·20$. The *X*-ray diagram showed that the solid was now mainly amorphous although some of the stronger lines of the original crystalline compound still showed up faintly.

It is clear from the above that decomposition caused by washing with small amounts of water is only slight, and is inadequate to explain such high R values as 0·886, as very little wash-liquor was used in separating the solids in dry state. Use of only a small amount of water seems to have had quite a different result. It has led to incomplete removal of the original mother-liquor which on drying has led to separation of some solid $Al_2O_3,2SO_3,11H_2O$ or even of $Al_2(SO_4)_3,16H_2O$ which is the most likely explanation of ratios less than 0·833. On equilibration over the mother-liquor the original amount of mother-liquor should be re-formed so that the equilibrated solids should have compositions corresponding to mixtures of $5Al_2O_3,6SO_3,46H_2O$ with saturated solution of the same composition as that over which equilibration had taken place. Thus if the dry solid of Table II (p. 2250) with $R = 0·824$ had retained 5% of mother-liquor it would have had the composition Al_2O_3, 26·80; SO_3, 25·26% after equilibration. In the case of the dry solid of Table II with $R = 0·815$ an original content of 4% of mother-liquor would give for the equilibrated solid a composition Al_2O_3, 27·04; SO_3, 25·57%. The calculated values for SO_3 tend to be lower than those found, which probably means that equilibration was not fully established. Conditions would actually be more complex than has been assumed in these calculations because of (*a*) slight hydrolysis of the original solid during the washing with even a very small amount of water, (*b*) deposition on the original solid of less soluble basic salt formed by hydrolysis of the mother-liquors being removed by the washing, (*c*) possible precipitation of some of the dissolved salts present in the adhering mother-liquor in cases where alcohol had been used in the washing. For these three reasons the contaminating material present in the washed, air-dry solids would tend to be more basic than would the evaporation residue of some of the original mother-liquor. The equilibrated solids would not represent true equilibrium conditions in the sense originally thought but only an approximation to this. The few cases in which dry solids were obtained with ratios higher than 0·833 are adequately accounted for by the almost certain presence of amorphous material, as the notes to Table II show. Admixture of glassy or amorphous with crystalline material, unless the former is present in very large amount, has such a small effect on the *X*-ray diagrams that it is often hard to draw conclusions from such diagrams as to the presence or absence of amorphous matter.

The compound $5Al_2O_3,6SO_3,xH_2O$ occurs in at least two different stages of hydration, but it seems clear from the tie-line graphical evidence and from the behaviour of air-dry solids on equilibration that only the hydrate in which x has the value 46 is stable in contact with solution at 25°. This hydrate occurs as slender prisms, probably monoclinic, which are thin rhombohedra. These show straight extinction when on edge, and when lying flat extinguish at an angle of 25° to the length of the prism and parallel to an end face. $5Al_2O_3,6SO_3,46H_2O$ tends to lose water on exposure to the air at ordinary temperatures to give $5Al_2O_3,6SO_3,40H_2O$. This formula was confirmed by examination of the preparation of Table II which had $R = 0·836$. It had been kept for 5 years in a lightly corked tube. It was placed in a crucible and left exposed to the air at a temperature of about 22°. Weighings at intervals during 50 hours showed that it was neither losing nor gaining weight. Analysis gave Al_2O_3, 29·76; SO_3, 28·07%; $R = 0·832$ (Calc. for $5Al_2O_3,6SO_3,40H_2O$: Al_2O_3, 29·83; SO_3, 28·07%. Calc. for $5Al_2O_3,6SO_3,39H_2O$: Al_2O_3, 30·14; SO_3, 28·37%). The lower hydrate so formed is crystalline and has a characteristic *X*-ray diagram quite different from that of the higher hydrate. It is, however, readily reconverted into the higher hydrate and both changes can occur at room temperature according to the relative humidity of the air. We have found that a specimen of $5Al_2O_3,6SO_3,xH_2O$, contained in a corked tube, changed backwards and forwards from the higher to the lower hydrate as shown by taking its *X*-ray diagram at intervals of several months or years. At one time we thought that both hydrates could exist in contact with solution at 25°, as there were indications of two solubility curves. The solution–moist solid tie lines do not support this view, however, and it seems clear that the appearance of two curves was caused by supersaturated conditions having persisted in some cases. There are indications that a more hydrated form of this salt $5Al_2O_3,6SO_3,60H_2O$ may be able to separate from very dilute solutions (see Note 8 to Table II).

The crystal structure of $5Al_2O_3,6SO_3,46H_2O$ is unknown, but there was a possibility of the existence

of stereoisomeric forms if the distribution of OH and H_2O was not random in any octahedral structures centred round aluminium ions which might be present (see p. 2252). This was tested for directly as follows. A solution (Al_2O_3, 8·6; SO_3, 13·0%) capable of depositing a considerable amount of $5Al_2O_3,6SO_3,46H_2O$ was prepared and allowed to stand without stirring at room temperature. Periodically the crystals which had separated from the solution were filtered off, washed, and air-dried. In this way seven fractions were obtained. The *X*-ray diagrams as well as the microscopic appearance of the first and the seventh fraction gave no indications of the separation of stereoisomers.

A precisely similar experiment was carried out with the compound $Al_2O_3,2SO_3,11H_2O$ since this might be a sort of double salt $[Al(H_2O)_6][Al(OH)_3H_2O)_4][SO_4]_3$, in which case there was also a possibility of the existence of stereoisomers. A solution containing Al_2O_3, 8·5; SO_3, 18·3% was used and five fractions of the solid were obtained. The first and the fifth fraction were identical as regards *X*-ray diagrams and optical properties.

With random distribution of hydroxyl groups in octahedral structures there would be no difference between $[AlOH(H_2O)_5][SO_4]_2$ and $[Al(H_2O)_6][Al(OH)_3(H_2O)_4][SO_4]_2$. When $Al_2O_3,2SO_3,11H_2O$ was treated at room temperature, or at 25°, with a concentrated solution of ammonium sulphate [1 g. of basic salt, 7·5 g. of $(NH_4)_2SO_4$, 10 c.c. of H_2O] separation of alum crystals began almost at once and was complete after a few days, being almost quantitatively that required by a reaction $2[AlOH(H_2O)_5]^{\cdot\cdot} \rightleftharpoons [Al(H_2O)_6]^{\cdot\cdot\cdot} + [Al(OH)_3(H_2O)_4]$.

Small amounts of semi-colloidal basic products also separated but, after being stirred, they could be pipetted away, with the solution, from the alum crystals. Since $Al_2O_3,2SO_3,11H_2O$ dissolves readily in cold water, this formation of alum is most likely due to the above disproportionation occurring in the solution and is no indication that $Al_2O_3,2SO_3,11H_2O$ really has the structure $[Al(H_2O)_6][Al(OH)_3(H_2O)_4][SO_4]_2$; indeed, *X*-ray single-crystal work on this compound shows that this structure is impossible.

$5Al_2O_3,6SO_3,46H_2O$ also gave alum crystals quite rapidly when similarly treated with ammonium sulphate, almost exactly one-eighth of the aluminium of a preparation having $R = 0·8$ appearing as alum. Disproportionation in the above sense is hastened by the separation of alum.

The experiments just quoted were carried out originally to see whether any double salts of $Al_2O_3,2SO_3,11H_2O$ or of $5Al_2O_3,6SO_3,46H_2O$ with ammonium sulphate could be obtained and showed that they could not.

Characteristic crystals of $5Al_2O_3,6SO_3,46H_2O$, giving a good *X*-ray diagram have been obtained by the action of sulphuric acid upon aluminium hydroxide. 20 G. of $AlCl_3,6H_2O$ in 100 c.c. water were precipitated cold by 78 c.c. of 3·2N-ammonia. The washed precipitate was added to 120 c.c. of 1·02N-sulphuric acid. After 24 hours at room temperature with occasional shaking, much of the hydroxide had dissolved, and after another 10 days the undissolved portion was mainly crystalline. 5 C.c. of 2N-hydrochloric acid were added in the hope of dissolving a small amount of residual alumina but some of this becomes very insoluble in acid on standing, and even after the mixture had been kept for 3 months, some was still mixed with the coarse crystals of basic salt. The latter were separated by decantation and washing with cold water from most of the hydroxide, but some of this was almost certainly still present. The air-dry crystals contained Al_2O_3, 29·38; SO_3, 25·03%; $R = 0·92$; yield 0·59 g.

The solubility curve of any solid phase xAl_2O_3,ySO_3,zH_2O in the system Al_2O_3–SO_3–H_2O should be a closed curve enclosing the point representing the composition of the dry solid. It is probable that the two-liquid system I (see p. 2257) is metastable towards $5Al_2O_3,6SO_3,46H_2O$ until it, in its turn, becomes metastable towards $5Al_2O_3,3SO_3,32H_2O$. There would, in this case, be no stable point of intersection of the solubility curve of $5Al_2O_3,6SO_3,46H_2O$ with the curve of two-liquid system I. It is important to bear in mind that a solid phase xAl_2O_3,ySO_3,zH_2O can only separate from solutions or mixtures having compositions which fall within its closed solubility curve. All points outside the latter correspond to mixtures which are unsaturated towards the compound in question. The numerous cases, met with during the examination of two-liquid system I, in which $5Al_2O_3,6SO_3,46H_2O$ appeared as an additional phase, suggest that one part of the metastable portion of the solubility curve of $5Al_2O_3,6SO_3,46H_2O$ probably cuts through the solubility curve of two-liquid system I and would eventually join up with the stable portion of the solubility curve of $5Al_2O_3,6H_2O,46H_2O$ after passing round the point corresponding to the latter composition (see Fig. 2).

$5Al_2O_3,6SO_3,46H_2O$ can exist up to at least 50° and was obtained at this temperature in an attempt to prepare "aluminite." A solution (115 g.) prepared by method (iii) and containing approx. Al_2O_3, 8·6; SO_3 13·0% was heated in a small conical, tightly corked flask held partly immersed in a thermostat adjusted to 50°. The mixture was inoculated with a very small amount of "aluminite." Separation of solid phase was very slow, but there was a considerable quantity after 24 days in the form of small, well-formed prisms which extinguished at angles ranging between 16° and 34° to the length. As the solid did not seem to be increasing in amount, some of the clear solution was pipetted out for analysis (temp. 50·3°), and the solid was then filtered off on a Buchner funnel and washed with a small amount of water, followed by absolute alcohol. Wt. of air-dry solid 1·609 g.; it contained: Al_2O_3, 27·93; SO_3, 26·58%; $R = 0·824$, and the *X*-ray diagram showed it to be $5Al_2O_3,6SO_3,xH_2O$. The solution contained: Al_2O_3, 8·67; SO_3, 13·36%, and this is less acidic than the corresponding solution at 25°, whereas the reverse would be expected. This may indicate that the 46-hydrate is metastable towards the 40-hydrate at 50°. In this method of heating, considerable loss of moisture through the cork occurred and in this case separation of solid must have been mainly dependent upon such loss.

A lower hydrate, $5Al_2O_3,6SO_3,36H_2O$, was obtained as follows at approx. 88°. 2750 G. of solution (Al_2O_3, 7·8; SO_3, 11·6%) were heated in a large lipless beaker covered by a clock-glass and standing in an oil-bath heated to 90°. The solution was not inoculated but slowly deposited a solid in the form of minute prisms showing straight extinction. Separation appeared to have stopped after 12 days' heating, during which time the total volume of mixture had decreased by about 500 c.c. owing to evaporation. The solid was filtered off, washed with cold water, and air-dried. The yield was 260 g. (Found: Al_2O_3, 31·22; SO_3, 29·22%; $R = 0·838$. $5Al_2O_3,6SO_3,36H_2O$ requires Al_2O_3, 31·14; SO_3,

TABLE II.

$5Al_2O_3,6SO_3,xH_2O$ *at* 25°.

(*w* = wt. %; *m* = molecular %.)

Solution.				Moist solid.				Dry solid.		Equilibrated solid.		Time shaken at 25°			
Al_2O_3.		SO_3.		Al_2O_3.		SO_3.		Al_2O_3.	SO_3.	Al_2O_3.	SO_3.	(weeks).	*R* of solid.	*R* of solution.	Note.
w.	*m.*	*w.*	*m.*	*w.*	*m.*	*w.*	*m.*	*w.*	*w.*	*w.*	*w.*				
8·57	1·92	18·11	5·12	14·83	3·65	20·87	6·56	—	—	—	—	2	—	—	
7·25	1·56	15·20	4·16	—	—	—	—	27·45	26·84	27·03	26·43	4·5	0·802	0·375	
7·16	1·53	15·11	4·12	18·52	5·08	26·40	9·24	—	—	—	—	5	—	—	(1)
7·17	1·53	14·97	4·08	15·90	3·93	19·89	6·26	—	—	—	—	4	—	—	
6·51	1·35	12·49	3·31	22·46	6·23	23·14	8·19	—	—	—	—	5	—	—	
5·85	1·20	11·80	3·08	17·98	4·54	19·84	6·39	—	—	—	—	8	—	—	(2)
5·76	1·18	11·76	3·07	18·91	4·88	20·69	6·81	—	—	—	—	13	—	—	(2)
5·55	1·13	11·13	2·88	15·88	3·85	18·28	5·65	27·19	26·48	—	—	14	0·805	0·392	(3)
4·57	0·89	7·19	1·78	17·86	4·44	18·38	5·82	27·17	26·10	27·05	25·98	2·5	0·817	0·500	
4·55	0·90	9·04	2·28	—	—	—	—	28·55	27·71	—	—	9	0·808	0·395	(4)
4·40	0·87	8·70	2·18	16·84	4·13	18·34	5·73	29·13	28·35	—	—	6	0·806	0·399	(5)
4·27	0·84	7·92	1·97	20·91	5·59	21·64	7·38	—	—	—	—	7·5	—	—	
4·07	0·79	7·38	1·83	—	—	—	—	27·04	25·85	—	—	12	0·820	0·432	(4)
3·94	0·75	5·44	1·32	17·95	4·43	17·65	5·55	—	—	—	—	8	—	—	(6)
3·79	0·73	6·96	1·71	18·91	4·81	19·51	6·34	27·16	26·31	26·93	26·10	7·5	0·810	0·427	
3·76	0·72	6·27	1·53	19·78	5·11	19·82	6·53	—	—	—	—	11·5	—	—	
3·02	0·57	5·58	1·35	17·76	4·39	18·06	5·69	—	—	—	—	18 days	—	—	
2·97	0·56	5·70	1·38	—	—	—	—	26·93	26·13	—	—	16	0·809	0·406	
2·86	0·54	5·62	1·36	—	—	—	—	27·06	26·04	27·00	25·98	16	0·815	0·397	
2·91	0·55	5·34	1·29	—	—	—	—	27·31	25·83	—	—	7	0·829	0·426	(4) (7)
2·81	0·53	5·26	1·26	—	—	—	—	27·55	25·85	—	—	29	0·836	0·421	(4) (7)
2·65	0·50	4·84	1·16	19·32	4·93	19·36	6·30	—	—	—	—	19	—	—	
2·57	0·48	3·51	0·83	18·07	4·29	13·96	4·23	—	—	—	—	2	—	—	(8)
2·33	0·43	4·52	1·08	—	—	—	—	27·23	26·04	—	—	10	0·820	0·398	(4)
2·34	0·44	4·00	0·95	—	—	—	—	28·73	25·45	27·69	24·52	19	0·886	0·463	(9)
2·37	0·44	3·49	0·82	—	—	—	—	30·72	20·70	28·45	19·18	13·5	1·16	0·537	(10)
2·16	0·40	3·66	0·87	20·93	5·51	20·42	6·86	27·38	26·06	26·85	25·55	15	0·824	0·460	
2·08	0·38	3·74	0·88	—	—	—	—	27·10	25·90	—	—	13	0·821	0·432	(4)
1·55	0·28	2·54	0·59	16·21	3·78	14·10	4·19	—	—	—	—	23	—	—	(11)
—	—	—	—	—	—	—	—	29·38	25·03	—	—	—	0·92	—	(12)
1·24	0·23	2·19	0·51	—	—	—	—	29·03	24·00	26·52	21·76	15·5	0·949	0·451	(8)
—	—	—	—	—	—	—	—	29·88	24·65	—	—	—	0·951	—	(13)

Notes to Table II. The mixtures for all the experiments in Table II were prepared by Method (iii) (see p. 2240).]—(1) Two mixtures of suitable composition, on either side of the transition point, were prepared, inoculated with $Al_2O_3,2SO_3,11H_2O$ and $5Al_2O_3,6SO_3,46H_2O$, respectively, and shaken for 2 weeks at 25°. Good crops of each compound had by then separated from their respective mixtures which were then combined. Crystals of both compounds could be distinguished in the final mixture after a further 3 weeks' shaking.

(2) The same original mixture analysed after 8 and 13 weeks' shaking.

(3) Mixture kept for 70 months at room temperature after preparation, and some of it was then shaken for 14 weeks at 25° with the results shown.

(4) These mixtures had been inoculated with 0·01 g. of "aluminite" but the solid separating was entirely $5Al_2O_3,6SO_3,46H_2O$. As the amount of this ranged from 2 to 6·5 g., any effect due to the aluminite, if still present as such, on the analyses would be inappreciable. The mixture giving the solution of Al_2O_3, 4·07; SO_3, 7·38% had been heated considerably during the preparation (see p. 2257).

(5) After exposure of a weighed amount in a crucible to the air at room temperature for 3 weeks it had lost more water—the weight having apparently become constant—and then contained Al_2O_3, 29·48; SO_3, 28·70%.

(6) This mixture had been inoculated with Werner's supposed $[Cr(OH)_2(H_2O)_4]_2[SO_4]$ (see p. 2253).

(7) The same original mixture analysed after 7 and after 29 weeks.

(8) The same original mixture used for these two experiments inoculated with 0·5 g. of $5Al_2O_3,6SO_3,40H_2O$. After 2 weeks' shaking some of the mixture was used for the first analysis. The solution was then very supersaturated and the tie-line suggests that some glassy solid was present along with $5Al_2O_3,6SO_3,xH_2O$. The rest of the mixture was left at room temperature for 11 weeks and then shaken at 25° for 15·5 weeks before the second analysis. The solid phase of this experiment was relatively coarse with some good crystals of $5Al_2O_3,6SO_3,46H_2O$. There were, however, microscopic and *X*-ray indications of the probable presence of a considerable proportion of glassy solid. The glassy solid corresponding to a solution of composition Al_2O_3, 1·24; SO_3, 2·19% would contain about Al_2O_3, 30·2; SO_3, 17·5%. A mixture of one-third of this with two-thirds of $5Al_2O_3,6SO_3,46H_2O$ would contain Al_2O_3, 28·8; SO_3, 23·4%, which is very close to the composition of the dry solid of the present experiment. Now the solid had been washed with cold water only, and exposed to the air for 20 hours before analysis, so it may well have lost only adhering water. The gain of water on equilibration could be accounted for very closely if the $5Al_2O_3,6SO_3,46H_2O$ had absorbed water to form a new hydrate with $60H_2O$. We have no other evidence for such a hydrate, but the case of hydrobasaluminite (see p. 2265) shows that some of the basic aluminium sulphates readily form labile hydrates containing large amounts of water. The ease with which some of these hydrated basic salts gain and lose water is shown by the behaviour of the present specimen which had been kept in a corked tube. It gave quite a good *X*-ray diagram. This was first taken 9 weeks after preparation and was that of $5Al_2O_3,6SO_3,40H_2O$. Fresh *X*-ray examination 6 weeks later gave the diagram of $5Al_2O_3,6SO_3,46H_2O$, and a year later a new *X*-ray diagram showed that the solid had again lost water to form $5Al_2O_3,6SO_3,40H_2O$.

(9) The mixture (21 g.) was inoculated with 0·0124 g. of "aluminite." This had caused no crystallisation after 14 weeks' shaking at 25°, but much of the "glassy" solid of the two-liquid system I (see p. 2257) had separated among which the "aluminite" crystals were visible. After filtration, the "glassy" solid readily dissolved in a little dilute acid, leaving the crystals, which after being washed and air-dried weighed 0·0126 g., while the solution contained Al_2O_3, 5·25; SO_3, 6·38%, which gives a point on the curve of two-liquid system I. Aluminite used for inoculation can evidently remain unaltered for long periods. The aluminite crystals were returned to the solution (now about 14 g.), and the mixture shaken for a further 19 weeks at 25°. 1·12 G. of air-dry solid were then obtained on filtering the mixture, and it consisted of fairly large well-formed prisms of $5Al_2O_3,6SO_3,46H_2O$ mixed with a small proportion of what looked like the glassy solid of two-liquid system I. The equilibrated composition is near to that needed for such a mixture containing 20% of the glass.

(10) The solid phase in this experiment consisted mainly of the glassy solid of two-liquid system I, though the *X*-ray diagram showed that some $5Al_2O_3,6SO_3,46H_2O$ was present. Both solution and equilibrated solid points fit on the curve of two-liquid system I.

(11) See Note (6) to Table III (p. 2259).

(12) See p. 2249 for details of preparation.

(13) A solution from which glassy solid had separated at 25° was filtered and contained Al_2O_3, 4·88; SO_3, 5·77%. After standing at room temperature for 3 years a small amount of solid (0·22 g.) had separated consisting of a mixture of good prisms with a considerably smaller proportion of the glassy solid. The *X*-ray diagram was that of $5Al_2O_3,6SO_3,46H_2O$.

29·30%). This *compound* appears to be identical with $Al_2O_3,SO_3,6{\cdot}78H_2O$ (see p. 2252). The mother-liquors from the solid contained Al_2O_3, 6·63; SO_3, 11·4%; $R = 0{\cdot}455$.

Rammelsberg (*Pogg. Ann.*, 1838, **43**, 583) analysed crusts deposited on the sides of a glass bottle in which dilute sulphuric acid, saturated with aluminium hydroxide, had been kept for many years. He considered that they consisted of $3Al_2O_3,4SO_3,30H_2O$. It seems more likely that they were a mixture of $5Al_2O_3,6SO_3,46H_2O$ and $Al_2O_3,2SO_3,11H_2O$. An equimolecular mixture of these would have a composition corresponding to $3Al_2O_3,4SO_3,28{\cdot}5H_2O$.

Compounds with $Al_2O_3/SO_3 = 1{\cdot}0$ (Plate, Nos. 5—8).

(1) $Al_2O_3,SO_3,9H_2O$.—The best known and best defined of all the basic aluminium sulphate minerals is "aluminite," $Al_2O_3,SO_3,9H_2O$. This occurs in a number of localities, usually as white chalky-looking nodules, composed of minute well-formed prisms. These nodules generally occur in a clayey material, and the field indications are that the "aluminite" has resulted from

the action of sulphuric acid formed by oxidation of pyrities or in other ways on clay or marl at quite ordinary or moderate temperatures. In one specimen, of unknown origin, in our collection it occurs as soft powdery patches surrounded by crystals of gypsum. " Aluminite " is a perfectly definite compound of fixed composition and giving a characteristic *X*-ray diagram. We have taken the *X*-ray spectra of three specimens of " aluminite " of quite different origins, one from the British Museum collection and two from our own, and find them to be identical. This has been confirmed by Dr. M. Hey and Mr. F. A. Bannister who have examined some other specimens also with the same result. The specimens examined by us were : (i) " Aluminite " B.M. 425 from Halle, Saxony, bought by the Museum from H. Heuland in 1837. This is not " type material " although the original " aluminite " was discovered near Halle, Saxony, about 1730. (ii) " Aluminite " from Red Desert Region, Sweetwater County, Wyoming, U.S.A. (iii) " Aluminite " from an old collection of minerals presented to the University of Reading. It included many fine specimens from famous localities but many had lost their labels. This specimen which we identified was one of these, so the locality from which it came is unknown. The " aluminite " is associated with crystals of gypsum, $CaSO_4,2H_2O$, in the specimen as well as with some clayey or perhaps bauxitic material.

Specimens (ii) and (iii) were analysed : The former contained 1·76% of material insoluble in cold concentrated hydrochloric acid after 30 minutes (dried at 105°); this consisted chiefly of very well-rounded quartz grains together with a little clayey material. The composition of the rest of the mineral, free from insoluble matter, was Al_2O_3, 30·03; SO_3, 23·32%; $R = 1·01$ (Calc. for $Al_2O_3,SO_3,9H_2O$: Al_2O_3, 29·65; SO_3, 23·26%). Specimen (iii) contained only 0·2% of material insoluble after digestion with 2N-hydrochloric acid; the rest of the mineral contained Al_2O_3, 30·28; SO_3, 23·10%; $R = 1·028$. Calcium, magnesium, and alkali metals were absent. The slight excess of alumina in both (ii) and (iii) is possibly due to extraction of a small amount from the associated clayey or bauxitic matter. There are no valid reasons for thinking that *R* of the pure mineral is other than 1·0 or that it is a solid solution.

Aluminite dissolves in acid much less readily than does $5Al_2O_3,6SO_3,xH_2O$.

Aluminite (iii) was interesting for a special reason. Material from one corner of the specimen gave an *X*-ray diagram entirely different from that of the aluminite with which it was first confused. Messrs. Bannister and Hey have clarified the situation by finding that material giving this new *X*-ray diagram is associated with aluminite on a number of specimens of this mineral from various localities. It has also been found in notable quantities in the Northamptonshire oolitic ironstone (Bannister and Hollingworth, *Nature*, 1948, **162**, 565). Its nature is discussed on p. 2265.

We have made many attempts to prepare aluminite at 25° by seeding with it a wide range of solutions from which $5Al_2O_3,6SO_3,46H_2O$ will crystallise. All these attempts were unsuccessful although the aluminite appeared to remain unaltered by such solutions for many weeks [see, *e.g.*, Note (9) to Table II]. Attempts to prepare it at higher temperatures have also failed, as have those in which dilute solutions of aluminium sulphate were treated with calcium carbonate.

Berzelius (" Lehrbuch der Chemie," Dresden, 1826, **2**, ii, 684) said that he got $Al_2O_3,SO_3,9H_2O$ by adding ammonia to a solution of aluminium sulphate to alkaline reaction, but Bley (*Annalen*, 1854, **89**, 174) said the product was more basic. Our experience shows that only gels of indefinite composition are obtained by such methods. The substance stated to be $Al_2O_3,SO_3,6H_2O$ by Böttinger (*ibid.*, 1888, **244**, 224) and obtained by heating an aqueous solution of aluminium sulphate and sodium chloride to 130—140° in a sealed tube would almost certainly have contained sodium and was probably an " alunite " (see p. 2254).

(2) Al_2O_3,SO_3,xH_2O (*possibly* $6Al_2O_3,6SO_3,40H_2O$).—This was obtained by heating to 70° 115 g. of a solution containing approx. Al_2O_3, 8·6; SO_3, 13·0% as in the experiment on p. 2249. Separation of solid was slow but after 15 days there was much of it in the form of small prisms showing straight extinction. The clear solution contained Al_2O_3, 7·00; SO_3, 12·36%. The solid, filtered on the pump and washed with cold water (50 c.c.) followed by alcohol (30 c.c.), weighed 7·8 g. after air-drying. A second crop of solid as small compact nodules of prisms was obtained after further 5 weeks' heating at 70° (Found, for 1st crop : Al_2O_3, 33·33; SO_3, 26·31%; $R = 0·994$. For second crop : Al_2O_3, 33·76; SO_3, 26·28%; $R = 1·008$. Calc. for $Al_2O_3,SO_3,6·78H_2O$: Al_2O_3, 33·56; SO_3, 26·31%). The *X*-ray diagram of this compound was found to be identical with that given by $5Al_2O_3,6SO_3,36H_2O$ (see p. 2251). Both preparations looked very good microscopically and had all the appearance of being pure compounds. Both consisted of small, clear, well-formed prisms and were indistinguishable. There were no signs of the presence of any amorphous material. The identity of their *X*-ray diagrams may arise in a similar way to that shown by members of the alunite group having widely different compositions. $Al_2O_3,SO_3,4H_2O$, $Al_2O_3,SO_3,6·78H_2O$, and $5Al_2O_3,6SO_3,36H_2O$ were all prepared in very much the same way at very similar concentrations, so that they may all have some structural similarity. The constitution of alunite is well established (see p. 2254). It dissolves in hydrochloric acid with considerable difficulty even when in a fine state of division. Of the other basic aluminium sulphates, $Al_2O_3,SO_3,4H_2O$ most resembles alunite in its resistance to acid. Similar chains of AlO_6 octahedra may be present in both compounds linked together criss-cross by the SO_4 ions, the proportions of which differ in the two compounds. On this basis $Al_2O_3,SO_3,4H_2O$ may perhaps be written $[Al_2(OH)_4]SO_4,2H_2O$, the $2H_2O$ being fitted into cavities in the lattice. Compounds with other formulæ are easily derived from a structure of the type $[Al_2(OH)_4]SO_4 + xH_2O$ by similar processes to those which appear to operate in the alunite group. Thus, starting with $[Al_{12}(OH)_{24}SO_4]_6 + 21H_2O$, if 2 of the 12 Al positions are vacant one gets $[Al_{10}(OH)_{18}(H_2O)_6][SO_4]_6 + 21H_2O$ which is $5Al_2O_3,6SO_3,36H_2O$. Compounds with higher *R* values can be derived from this not only by filling the vacant Al positions in the octahedral band kation but also by replacing SO_4'' by $[Al(OH)_4]'$. This

second method gives compounds containing a higher proportion of water. A product corresponding to $6Al_2O_3,6SO_3,40{\cdot}67H_2O$ would be given by admixture in the molar ratio 1 : 2 : 2 of $[Al_{11}(OH)_{33}(H_2O)_3][SO_4]_5[Al(OH)_4],21H_2O$, $[Al_{10}(OH)_{19}(H_2O)_5][SO_4]_5[Al(OH)_4],21H_2O$, and $[Al_{10}(OH)_{18}(H_2O)_4][SO_4]_6,21H_2O$, respectively, and this would contain Al_2O_3, 33·56; SO_3, 26·31%.

It is of interest that the loss of weight at 100° (see below) would correspond almost exactly to loss of the $21H_2O$ in the above formulation. The small difference in compositions between the first and the second crop of Al_2O_3,SO_3,xH_2O indicates that it was probably chance that gave a product with R so close to unity.

This case merits further investigation, but everything points to its being a genuine one of solid solution formation. It seems clear that $5Al_2O_3,6SO_3,40H_2O$ and $5Al_2O_3,6SO_3,46H_2O$ do not give rise to solid solutions (see p. 2248) although some relationship to $5Al_2O_3,6SO_3,36H_2O$ might reasonably be expected. This might well be due to instability being caused in the more hydrated lattices both by (*a*) vacant Al positions in the AlO_6 band kations and by (*b*) lowering the total charges on the kations and anions by any replacement of $[SO_4]''$ by $[Al(OH)_4]'$. The two higher hydrates may therefore be kept rigidly of the form $[Al_{10}(OH)_{18}(H_2O)_2][SO_4]_6 + 29$ or $35H_2O$. If this is correct it follows that $5Al_2O_3,6SO_3,36H_2O$ belongs to a somewhat different series from the two more hydrated salts, since its band kation contains 6 octahedra for $6[SO_4]''$ ions instead of only 5.

(3) $Al_2O_3,SO_3,4H_2O$.—Another *compound* $Al_2O_3,SO_3,4H_2O$ was readily obtained as follows. A solution in a silica beaker prepared by method (iii) and containing approx. Al_2O_3, 8·6; SO_3, 13·0% was placed in another beaker of water heated nearly to 100°. Separation of white solid began fairly soon, but at a slow rate which became more and more rapid as the amount of solid increased and was complete after a week. Water lost by evaporation was periodically replaced but 20% had been lost by the mixture and was not replaced when the experiment was stopped and the solid separated. The rather viscous filtrate gave no precipitate on dilution with water. The solid was washed on the pump with water and air-dried; yield 10·33 g. from 116 g. of original mixture. The mother-liquor contained Al_2O_3, 7·40; SO_3, 14·94%, and the air-dry solid, Al_2O_3, 40·14; SO_3, 31·39%; $R = 1{\cdot}003$ ($Al_2O_3,SO_3,4H_2O$ requires Al_2O_3, 40·16; SO_3, 31·42%).

The solid is strongly doubly refracting though individual crystals are very minute and too small to examine; they are probably orthorhombic. Its *X*-ray diagram is quite different from that of aluminite and of $Al_2O_3,SO_3,7H_2O$ and $5Al_2O_3,6SO_3,xH_2O$. It dissolves with great difficulty in acid. Heating for about 20 minutes with concentrated hydrochloric acid diluted with an equal volume of water is required, and digestion for several hours is needed with 2N-acid. Some of the solid and mother-liquor were shaken at 25° for 3 months and again separated for analysis. There had been little change of composition. The solution then contained Al_2O_3, 7·34; SO_3, 14·51%, and the air-dry solid Al_2O_3, 40·09; SO_3, 31·41%. Owing to the slow rate of solution of this solid it is doubtful whether these figures give a point on its 25° solubility curve. The air-dry solid after equilibration over the solution for 6 weeks had absorbed 2·2% of moisture. No more was taken up after another period of 6 weeks. This was all lost again after a few days' exposure to the laboratory air.

It has been shown by *X*-ray examination that the initial precipitate thrown down on heating such solutions as the above is amorphous. It is the glassy phase of two-liquid system I. In preparing $Al_2O_3,SO_3,4H_2O$ heating must be continued long enough to cause all traces of this amorphous material to become fully crystalline.

(4) $Al_2O_3,SO_3,5H_2O$.—Aluminite (ii) (p. 2252) lost 21·83% when heated to constant weight at 100—115°, allowance being made for the 2% of impurity assumed to lose nothing. Aluminite (iii) lost 20·0%. This corresponds closely to the formation of the *hydrate* $Al_2O_3,SO_3,5H_2O$, for which the calculated loss would be 20·93%. The product gave a striking and distinctive *X*-ray diagram. There were indications of a further halt at about $Al_2O_3,SO_3,2{\cdot}5H_2O$ at 150°, and at 200° the weight became constant with a total loss of 36·88%. This would correspond to the formation of $Al_2O_3,SO_3,2H_2O$ (Calc.: loss, 36·63%), but the *X*-ray diagram showed that the product was amorphous.

The fact that aluminite on dehydration does not, apparently, pass through the $Al_2O_3,SO_3,4H_2O$ stage is striking and suggests some important structural difference.

$Al_2O_3,SO_3,6{\cdot}78H_2O$ after being heated to constant weight at 100° corresponded to $Al_2O_3,SO_3,3\frac{1}{2}H_2O$, but *X*-ray examination showed that the product was amorphous.

$Al_2O_3,SO_3,4H_2O$ on dehydration to approximately constant weight first at 150° then at 200° lost 10·01% by weight in all. *X*-Ray photos were taken after heating to 150° and to 200°, but gave no indication of the formation or any lower hydrate. The lines of the original compound gradually disappeared as more and more amorphous material was formed. Even in the final product a few of these lines were still faintly visible.

The existence of a compound $[Al(OH)_2(H_2O)_4]_2SO_4 = Al_2O_3,SO_3,10H_2O$ could be reasonably expected but we have failed to obtain it. Among other methods tried without success was inoculation of suitable solutions with the corresponding chromium compound which, according to Werner (*Ber.*, 1908, **41**, 3447), can be obtained as a bright green, silky-looking, crystalline material by the action of pyridine on a solution containing chrome alum and sodium sulphate. The product obtained by following Werner's directions as closely as possible did not look crystalline, but, after air-drying, it contained Cr_2O_3, 38·3; SO_3, 19·25% (Calc.: Cr_2O_3, 36·89; SO_3, 19·42%), so it may have been essentially the compound which Werner claimed it to be. His method when applied to ammonium aluminium alum gave no precipitate at all.

The "Alunite" Group of Minerals and Compounds (Plate, Nos. 9 and 10).

The first-discovered and still the best-known member of this group is the potassium compound, $K[Al_3(OH)_6][SO_4]_2$, to which the name "alunite" strictly belongs. It occurs as a well-crystallised mineral in a number of localities and often in large quantities. Its high content of potassium makes it of considerable technical interest. During the past 50 years it has

become apparent that "alunite" is only one of a large number of minerals which are isomorphously related (Schaller, *U.S. Geol. Survey Bull.*, **1912**, **509**, 76; *Z. Kryst.*, **1912**, **50**, 106; *Amer. J. Sci.*, **1911**, **32**, 359).

Isomorphous replacement within the group can be of the ordinary simple kind where Na, NH_4, K, Rb replace each other or $[Fe_3(OH)_6]$ replaces $[Al_3(OH)_6]$, but compensatory replacement may also occur. Many of the alunite minerals are phosphates in which the higher valency of the PO_4 as compared with the SO_4 group is balanced by the presence of bivalent kations such as Pb, Sr, or Ba in place of alkali metals. The situation was greatly clarified by Hendricks's study of the crystal structure of alunite and the jarosites (*Amer. Min.*, 1937, **22**, 772). The crystal lattice contains endless bands of AlO_6 or FeO_6 octahedra in which each Al or Fe ion is surrounded by four hydroxyl ions and two oxygen atoms of SO_4 ions. The latter are in *trans*-positions in the octahedra. These are joined by their edges, two OH ions being shared by two octahedra. The unit cell of alunite contains the amount represented by the formula $K[Al_3(OH)_6][SO_4]_2$.

Hendricks showed that the alunite structure is retained when one of the six hydroxyl ions is replaced by a water molecule. The group $[Al_3(OH)_5(H_2O)]$ carries four positive charges, however, so that no potassium ion is required in order to balance the charges on the two $[SO_4]$ ions. The place of the potassium is therefore taken by another water molecule, and it was shown that the *X*-ray diagram of $H_2O[Fe_3(OH)_5H_2O][SO_4]_2$ was in fact very closely similar to that of jarosite, $K[Fe_3(OH)_6][SO_4]_2$. It is probable that the rhombs of $3Al_2O_3,4SO_3,9H_2O$ obtained by heating a 3% solution of aluminium sulphate to 250° (Athanescu, *Compt. rend.*, 1886, **103**, 271) correspond to this ferric compound.

According to our investigations other modifications of the alunite structure can occur. These are all, in a sense, an extension of Hendricks's replacement of one in six of the hydroxyl ions of the $[Al_3(OH)_6]$ or $[Fe_3(OH)_6]$ chain by H_2O. As our work has concerned aluminium compounds we shall refer only to these. Each OH of the chain ion which is replaced by H_2O corresponds to an extra positive charge on this ion. Survival of the alunite structure must be dependent upon the retention of the chain kation with 3 octahedra per unit cell and of two $[RO_4]$ ions.

Replacement of two out of six OH by H_2O would be possible if one $[SO_4]$ were replaced by $[PO_4]$ to give $H_2O[Al_3(OH)_4(H_2O)_2][PO_4][SO_4]$, but, as our experiments have related only to sulphates, we will not consider further this possibility.

Replacement of more than one of the six OH groups by H_2O without increasing the valency of the $[RO_4]$ ion beyond 2 is only possible if an aluminium ion is dropped from one of the octahedra. In this way the compounds $NH_4[Al_2(OH)_3(H_2O)_3][SO_4]_2$, $H_2O[Al_2(OH)_2(H_2O)_4][SO_4]_2$, and $H_2O[Al_2(OH)_4(H_2O)_2][Al(OH)_4]_2$ could originate. The empty octahedra and the OH and H_2O would doubtless occur in the octahedral chains with a statistical distribution. Assumption of these compounds in addition to those already mentioned as accepted by Hendricks has enabled us to account quantitatively and exactly for the composition of a number of preparations which give excellent *X*-ray diagrams although their composition differs widely from that usually attributed to alunite.

Empty octahedral positions are, of course, well known in aluminium compounds. In hydrargillite, $Al_2O_3,3H_2O$, one in three of such positions contains no aluminium ion. The octahedra in the chains of the alunite structure are held together strongly by the $[SO_4]$ ions, and this should facilitate the occurrence of empty octahedra.

Potassium, sodium, and ammonium alunites were first prepared by Mitscherlich (*J. pr. Chem.*, 1861, **83**, 455) by heating in sealed tubes to 230° solutions of the appropriate alum and additional aluminium sulphate to which the corresponding alkali hydroxide had been added to the point at which further addition would have caused a permanent precipitate. Ammonium alunite does not appear to be known as a mineral, though ammonio-jarosite $NH_4[Fe_3(OH)_6][SO_4]_2$ occurs naturally (Dana, "Text-book of Mineralogy," 4th edn., 1932, p. 769). Until about 20 years ago it was supposed that alunite had been formed in Nature at relatively high temperatures and pressures (Hintze, "Handbuch der Mineralogie," **1929**, I, 3, ii, 4183). This may have been the case with some occurrences of the mineral, but Leonard (*Econ. Geol.*, **1927**, **22**, 18) showed that alunite can be produced at atmospheric pressure and temperatures as low as 20°, and it is well known to those who handle quantities of hot, slightly basic, liquors of alums or aluminium sulphate that these deposit precipitates which are alunitic in nature.

It may be necessary, in order to prepare in the laboratory well-crystallised alunites with the composition required by the conventional formulæ, to use the sealed-tube technique, but preparations obtained at ordinary pressure and temperatures not above 100° are micro-, or even

more coarsely, crystalline and give *X*-ray diagrams like that of the mineral. Such preparations differ from the mineral in seldom, if ever, having a composition required by the simple formulæ. They are either more basic or less basic, and the water content is often very high, as can be seen from the preparations shown in Table IIA. These can all be explained satisfactorily in terms of mixtures of the compounds discussed above. This manner of representing the composition of the preparations is, of course, artificial. In reality there will be some sort of random distribution of all the ions which take part in the isomorphous replacement. The compound $H_2O[Al_2(OH)_4(H_2O)_2][Al(OH)_4]_2 = 2Al_2O_3,9H_2O$ is not known. Since it is necessary to assume the presence of a small proportion of V in all the preparations of Table IIA, it would appear that a small concentration at least of $[Al(OH)_4]$ ions must have been present in all the solutions involved. Measurements of the *X*-ray diagrams of these alunites are recorded in Table X (Appendix) because of their possible interest in connection with replacements occurring in the group.

Löwigite (Löwig, *Z. deut. geol. Ges.*, 1856, **8**, 247; Mitscherlich, *op. cit.*, p. 474), a somewhat ill-defined mineral found associated with alunite, has been given the formula $K_2SO_4,3Al_2O_3,3SO_3,9H_2O$. It is probable that this is actually an alunite and the above formula would be given exactly by the mixture of alunites: 1·2 mols. of $K[Al_3(OH)_6][SO_4]_2$ + 0·8 mol. of $K[Al_2(OH)_3(H_2O)_3][SO_4]_2$ + 0·2 mol. of $H_2O[Al_2(OH)_4(H_2O)_2][Al(OH)_4]_2$. Mr. F. A. Bannister has taken the *X*-ray diagrams of the British Museum specimen of löwigite and reports that it does, in fact, given the alunite diagram.

Further, the solid obtained by autoclaving at above 150° a concentrated solution of potassium alum in the " Kalunite " process for extracting alumina from alunite (B.PP. 397407—397412, 1933; Fleischer, *Amer. Inst. Min. Met. Eng.*, 1944, Tech. Publ. 1713; *Brit. Chem. Abs.*,

TABLE IIA.

Alunites.

Analysis of air-dry solids, %.							Same composition given by mixture of the " molecular " proportions indicated.*	
$(NH_4)_2O$.	K_2O.	Na_2O.	Al_2O_3.	Cl.	SO_3.	H_2O (diff.).		Note.
3·73	—	—	35·41	0·83	30·98	29·32	1·0 II*c* + 0·35 III + 0·535 V	(1)
2·91	—	—	35·42	0·34	30·10	31·31	1·0 II*c* + 0·68 III + 0·71 V	(2)
6·44	—	—	34·80	1·25	39·96	17·83	0·55 I*c* + 0·45 II*c* + 0·05 V	(3)
5·46	—	—	32·81	—	39·96	21·77	0·38 I*c* + 0·62 II*c* + 0·19 III + 0·077 V	(4)
4·24	—	—	35·37	—	40·85	19·55	1·0 I*c* + 0·566 III + 0·031 V	(5)
4·28	—	—	35·77	—	37·83	22·12	0·74 I*c* + 0·26 II*c* + 0·437 III + 0·163 V	(6)
—	11·33	—	29·46	—	38·77	20·44	0·17 I*b* + 0·83 II*b* + 0·007 IV + 0·052 V	(7)
—	9·62	—	29·52	—	38·62	22·24	0·16 I*b* + 0·84 II*b* + 0·185 III + 0·075 V	(8)
—	9·06	—	28·27	—	37·75	24·94	1·0 I*b* + 0·23 III + 0·105 V	(4)
—	—	5·77	31·26	—	39·17	23·80	0·2 I*a* + 0·8 II*a* + 0·315 III + 0·115 V	(4)
—	—	5·97	33·69	—	37·65	22·69	0·4 I*a* + 0·6 II*a* + 0·225 III + 0·145 V	(9)
—	—	5·65	34·66	—	40·37	19·32	0·83 I*a* + 0·17 II*a* + 0·385 III + 0·035 V	(10)

* Key to the compounds referred to in this column:

I*a* = $Na[Al_3(OH)_6][SO_4]_2$
I*b* = $K[Al_3(OH)_6][SO_4]_2$
I*c* = $NH_4[Al_3(OH)_6][SO_4]_2$
II*a* = $Na[Al_2(OH)_3(H_2O)_3][SO_4]_2$
II*b* = $K[Al_2(OH)_3(H_2O)_3][SO_4]_2$
II*c* = $NH_4[Al_2(OH)_3(H_2O)_3][SO_4]_2$
III = $H_2O[Al_2(OH)_3(H_2O)_4][SO_4]_2$
IV = $H_2O[Al_2(OH)_5(H_2O)][SO_4]_2$
V = $H_2O[Al_2(OH)_4(H_2O)_2][Al(OH)_4]_2$

In calculating the mixtures of these compounds which gave the same compositions as those found for the various preparations listed in Table IIA it was found simplest to take NH_4, K, or Na as unity and to divide it among compounds I and II. Then, by inspection and trial, the amounts of the other compounds which must be present were readily deduced, the hydroxyl equivalent to any chlorine present having been first calculated (see Note 2).

All the preparations of Table IIA dissolved in acid with considerably more difficulty than any of the other basic sulphates with the exception of $Al_2O_3,SO_3,4H_2O$. The ease of solution varies considerably according to the state of division of the preparation, and for amounts of 0·2—0·4 g. of solid the time required for solution in nearly boiling hydrochloric acid varied from about 10 minutes in 2N-acid to an hour in 10N-acid.

Notes to Table IIA.—All the preparations quoted in this table gave *X*-ray diagrams characteristic of alunite. Careful measurements disclosed small differences in the spacings and intensities of some of the lines (see Appendix, Table X).

(1) This is the alunite preparation described on p. 2275.

(2) 2 G. of the preparation of Note 1 were washed slowly on a funnel with 30 c.c. of cold water, then with alcohol, and air-dried. The analysis of the washed solid shows that, if the chlorine originally present is supposed to have been due to contaminating ammonium chloride, then only 59% has been removed

by the washing together with 15% of ammonium sulphate. In view of this result and the coarsely crystalline nature of the solid, the only reasonable conclusion to draw appears to be that the chlorine must be a constituent part of the alunite structure, replacing hydroxyl. The chlorine is slowly removed by hydrolysis but not much more readily than the ammonium.

This is one of only two cases in Table IIA where there is not perfect agreement between the water content, as well as all other constituents, as found by analysis and calculated for the mixture given in the table. The analytical composition corresponds to 15·52 mols. of H_2O per NH_4 ion, whereas the calculated figure is only 14·93 mols. It is quite likely that a small portion of the hydrolysis product had failed to crystallise fully and had retained, in consequence, too much water.

It may be significant, in this connection, that the only other preparation of Table IIA which did not give perfect agreement for all constituents between found and calculated figures was the preparation of potassium alunite containing 9·06% of K_2O. The analytical figures gave 7·2 mols. of H_2O per K ion, whereas the calculated figure for the mixture shown in Table IIA is only 6·83 mols. of H_2O. The washing with *hot* water may have led to the formation of some amorphous hydrolysis product.

(3) This solid was prepared in a similar manner to that of Note 1, but a larger proportion of basic double salt I had separated (4·30 g. as compared with 3·51 g.), so the basicity of the filtrate which was heated was less. 4·58 G. of alunite were obtained from this, and after 24 hours' heating it looked crystalline under the microscope though it was too fine for any double refraction to be seen.

(4) A solution was prepared containing approx. 8·6% Al_2O_3; 13·0% SO_3, that is to say, of the same composition as that which yielded the compound $Al_2O_3,SO_3,4H_2O$ after long heating to nearly 100° (see p. 2253). 20-G. lots of this solution were placed in three large test-tubes; to one was added 2 g. of ammonium sulphate and 5 c.c. of water, to another 2·64 g. of potassium sulphate and 5 c.c. of water, and to the third 2·16 g. of sodium sulphate and 5 c.c. of water. The mixtures were then placed in a beaker of boiling water. Solid began to separate very soon from each mixture, first from that containing potassium sulphate and last from that containing ammonium sulphate. After 5½ hours' heating in the boiling water the ammonium solid, though fine, was obviously crystalline. The other two solids were finer but looked crystalline though it was difficult to be certain whether there was any double refraction. The solids were then filtered hot. The ammonium solid was washed with 80 c.c. of cold water only and air-dried; its hot mother-liquor on standing deposited a considerable amount of alum. The potassium solid was washed with 70 c.c. of hot water, 10 c.c. of 50% alcohol, and finally with absolute alcohol, and air-dried. The sodium solid was washed with 60 c.c. of water, 10 c.c. of 50% and 10 c.c. of absolute alcohol, and air-dried. Yields were: NH_4 solid 2·624 g.; K solid 4·95 g.; Na solid 3·71 g.

(5) 22·5 G. of ammonium alum in 140 c.c. of water gently boiled in a beaker for about 26 hours, water lost by evaporation being replaced at intervals. The solid which had separated was fine but crystalline and was filtered off from the hot solution, washed with cold water, and air-dried; weight 0·736 g.

(6) 20 G. of solution (8·6% Al_2O_3; 13·0% SO_3) had been boiled for 2 hours. 1 G. of ammonium sulphate in 5 c.c. of water was added, and mixture shaken at 25° for 9 days; 4·46 g. of alum crystals which had separated were filtered off. After standing at room temperature for 48 hours, some more alum had crystallised out. The decantate from these was heated nearly to 100° for 30 hrs., and the minutely crystalline solid was then filtered from the hot mother-liquor, washed with 60 c.c. of cold water, and air-dried; yield 2·42 g.

(7) 2·7 G. of potassium hydroxide in 25 c.c. of water were added to 15·28 g. of potassium alum in 150 c.c. of water slowly with vigorous stirring. The mixture was filtered from a small amount of undissolved precipitate into a silica beaker which was immersed in a beaker of water kept at about 60°. Precipitate soon began to separate. After 16 hours' heating some fair-sized crystals were present. These were in the form of a right-angled wedge, the hypotenuse being the thin edge. Extinction was parallel to the hypotenuse. As this is one of the forms in which $5Al_2O_3,3SO_3,xH_2O$ (see p. 2266) separates, it is likely that the crystals consisted of this substance. After a further 4 days' heating all these wedge-shaped crystals had disappeared but the whole finely granular solid was crystalline and sparkled brilliantly when rotated between crossed nicols. After being heated to 60—90° for 11 days in all, the hot mixture was filtered and the solid washed with about 20 c.c. of water followed by absolute alcohol; weight of air-dry solid 5·09 g.

(8) Carried out as in the experiment to which Note 7 refers except that only 1·3 g. of potassium hydroxide were used and the mixture was heated for 5 weeks in a corked conical flask immersed in a thermostat kept at 70°. The solid was too fine to be sure from microscopic examination whether it was all crystalline. *X*-Ray examination showed that it was; yield 3·03 g.

(9) 9·7 G. of $Al_2(SO_4)_3,16H_2O$ and 4·9 g. of sodium sulphate decahydrate were dissolved in 100 c.c. of water, and 2 g. of sodium hydroxide in 15 c.c. of water were gradually added with vigorous stirring. The filtered solution was heated to 50° for 4 days. The solid which had separated did not look crystalline, and was shown to be completely amorphous by *X*-ray examination. About half was filtered off, and the rest of the mixture heated to 65° for 2 days. Square crystals had appeared after 2 days at 65°. In the hope that the proportion of square crystals might be increased, an additional 2·45 g. of sodium sulphate were added, but this made no difference. After a further 9 days' heating the solid was filtered off, washed with much water, then absolute alcohol, and air-dried; weight of solid, 2·14 g. After standing for a fortnight much of the doubly refracting $Na_2SO_4,Al_2(SO_4)_3,22H_2O$ had crystallised from the mother liquors.

(10) A solution of aluminium sulphate approximately saturated at the boiling point was boiled with γ-$Al_2O_3,3H_2O$ in the form of the so-called " Bayer hydrate " (hydrargillite) which always contains some sodium as an impurity. When no further hydrate appeared to be dissolving, the mixture was diluted and filtered, and the filtrate boiled for a long time. Small thin, nearly square, plates or aggregates of these separated having $R = 0·674$.

By working as above with 150 g. of $Al_2(SO_4)_3,16H_2O$ only 0·368 g. of the basic salt was obtained. The mother-liquor contained Al_2O_3, 9·39; SO_3, 20·91%; $R = 0·352$.

B, 1945, 153) is also stated to be $K_2SO_4,3Al_2O_3,4SO_3,9H_2O$. This also may well be an alunite and with 10·5 instead of $9H_2O$ the composition would be exactly matched by the mixture of alunites: 1 mol. of $K[Al_3(OH)_6][SO_4]_2$ + 1 mol. of $K[Al_2(OH)_2(H_2O)_2][SO_4]_2$ + 0·5 mol. of $H_2O[Al_2(OH)_2(H_2O)_4][SO_4]_2$.

Two-Liquid System I. The "Glassy Solid."

Solutions in equilibrium at 25° with $5Al_2O_3,6SO_3,46H_2O$ and containing less than about 4·9% Al_2O_3 and 9·1% SO_3 become milky on sufficient dilution (at room temperature) owing to separation of a still more basic product. The same substance can be obtained by spontaneous separation, without any dilution, from solutions of suitable composition prepared by method (iii) (p. 2240). It is also formed by boiling crystals of $5Al_2O_3,6SO_3,xH_2O$ with water. By using these three methods of preparation the solubility curve of this more basic material has been traced. The results are recorded in Table III.

This more basic material is amorphous or glassy. It is obtained in the form of relatively large glassy spheres or discs where separation has occurred slowly from solutions prepared by method (iii), either spontaneously, or as a result of very gradual dilution, extending over several weeks, of suitable concentrated solutions. These spheres or discs break with a conchoidal fracture and are isotropic when examined in polarised light. The basic material which separates quickly on rapid dilution of fairly concentrated solutions is seen under the microscope to consist of aggregates of very minute transparent discs, while the precipitate obtained by dilution of dilute solutions shows very little structure under the microscope. The material is found to be amorphous by *X*-ray examination, whether it is in the form of the large glassy spheres or of the more or less structureless precipitates.

The composition of the "glassy" or amorphous phase is variable and depends upon that of the solution from which it separates. Its water content is very sensitive to the humidity of the air with which it is in contact, varying continuously with this.

The "glassy" phases were analysed after filtration and washing followed by equilibration over the mother-liquors as described on p. 2243. The results so obtained have led to the conclusion that the "glassy" material represents the more concentrated phase of a two-liquid system. This appears to form a closed curve when plotted in the ordinary triangular diagram, as shown in Fig. 1. Although the more concentrated phase is "glassy" over the greater part of the region, it may be liquid in the ordinary sense of the word at the dilute end of the region where its water content is very high. The equilibrium "solids" corresponding to the most dilute solutions in Table III are rather soft.

Separation of the glassy phase of the two-liquid system on dilution of previously clear solutions can only occur if this dilution brings the composition within the area of the closed curve of the two-liquid system. The diluted solution will then break up into the appropriate glassy and liquid solutions. Now the lines joining points on the 25° solubility curve of $5Al_2O_3,6SO_3,46H_2O$ to the water point just fail to cut the curve of the two-liquid system, at 25°. Dilution at 25° would not therefore cause any separation of glassy solid. The curve of the two-liquid system and the other solubility curves will doubtless shift to the left-hand (or SO_3) side of the triangular diagram (corresponding to decreased solubility) with fall of temperature. Dilution at room temperature of a solution which was saturated with respect to $5Al_2O_3,6SO_3,46H_2O$ at 25° may well bring the composition to within the area of the two-liquid system at room temperature, with resultant precipitation of glassy solid.

Some change in the composition of the "glassy" solid is liable to occur, owing to further hydrolysis, when adhering mother-liquor is removed by washing with water. The solid will tend to become more basic. Washing of the "glassy" solids must for this reason be restricted as far as possible when separating them in a dry state for analysis and equilibration. This effect of the washing is one reason why solution, moist solid, and equilibrated solid points do not always fall on one straight line when plotted on the triangular diagram (see, *e.g.*, Note 11 to Table III). The effect on the composition of the glassy solid due to this cause appears as a rule to be less than that caused by heating the mixtures (see pp. 2258, 2260). Heating the mixtures affects the *slope* of the solution–moist solid tie-line as well.

Method (iii) is only suitable for preparing mixtures in the more concentrated region. If used for the more dilute region, solid (*viz.*, "glassy" phase) separates before all the aluminium has dissolved and it is not possible to separate the finely divided mercury by filtration. This may happen even in the more concentrated region if an attempt is made to obtain too large a proportion of the "glassy" phase. Preparation by the method of dilution has to be used for the less concentrated region, and large quantities of diluted solution must be prepared in some cases in order to obtain sufficient of the "glassy" phase.

All solutions in equilibrium with "glassy" solid become milky or turbid on dilution, more or less rapidly, according to circumstances. This shows that the curve of the two-liquid system is concave to the lines joining any point on this curve to the water point. A solution represented by any point on one of these lines will tend to break up into a more dilute solution and a corresponding "glassy" solid. Equilibrium solutions containing less than 0·5% Al_2O_3; 1·0% SO_3 only become faintly opalescent after very great dilution because in this region the curve of the two-liquid system is almost a straight line which runs practically to the water point.

Separation of the second (or "glassy") liquid phase is associated with some tendency for supersaturation to persist which is small in dilute solutions but considerable in the more concentrated and viscous ones.

Since the two-liquid system is probably entirely metastable towards crystalline compounds (see pp. 2249, 2260, 2264) there is always some tendency for such crystals to separate and complicate the situation.

Even when this does happen, analyses of the filtered solutions will generally give points which fall on the true (*i.e.*, not supersaturated) curve of the two-liquid system. Separation of crystalline material chiefly causes trouble in the study of the more concentrated region of the two-liquid system. The

tie-lines for this system are approximately parallel to one another. If an odd one cuts the others this may be due to the presence of some crystalline solid along with the " glassy " phase, although it occasionally happens that, for some reason, there has been lack of proper adjustment between the solution and the glassy solid so that the latter is not of uniform composition.

We know of no case where a two-liquid system of this kind has been systematically examined. Jones (*Trans. Faraday Soc.*, 1939, **35**, 1484) observed an isotropic material, similar to our " glassy " solid, in the system CaO–Al_2O_3–$CaSO_4$–H_2O. It was prepared by the action of lime-water in the cold on solutions of aluminium sulphate and was considered by Jones to be aluminium hydroxide gel with some lime in solution. Jones records n as 1·525—1·54 in some parts of the system and 1·48—1·49 in others (see Note 6 to Table III).

If all the mixtures in the region of the two-liquid system are prepared with little or no heating, the tie-lines are found to run approximately parallel to one another, while the solution and corresponding equilibrated dry (glassy) solid points lie on an elongated, roughly elliptical, closed curve (Fig. 1).

Mixtures in the more dilute region of the two-liquid system will actually deposit glassy solid if heated, but this does not apply to mixtures in the more concentrated region. The solid which has separated on heating usually redissolves again fairly soon after cooling to the original temperature.

The latter mixtures after being heated to 100° or even less for some time remain supersaturated for a considerably longer time when shaken at 25° than do mixtures which have not been heated. When glassy solid does separate at 25° from such heated solutions, the aqueous liquid soon adjusts itself to a point on the normal curve of the two-liquid system, but the composition of the glassy solid is generally too basic and may require a very lengthy period for proper adjustment. This too basic solid (after equilibration) may or may not fall on the curve of the two-liquid system but gives a tie-line which cuts across those of experiments in which the mixtures had not been heated. The behaviour indicates that heating has altered in some way the nature or relative concentration of the ionic or other species in solution. The composition of the glassy solid which separates is bound to reflect this alteration. The outermost layer of the glassy particles after they have been shaken for some time at 25° will no doubt have the composition which should correspond to that of the aqueous solution, but adjustment of composition throughout the whole glassy particle is a very slow process so that even after long shaking at 25° the bulk composition of the glassy solid remains abnormal in such cases.

TABLE III.

Two-liquid system I at 25°.

Solution.		" Glassy " Solid.							
		Moist.		Air-dry.		Equilibrated.		Time of shaking at 25°	
Al_2O_3, %	SO_3, %	Al_2O_3, %	SO_3, %	Al_2O_3, %	SO_3, %	Al_2O_3, %	SO_3, %	(weeks).	Note.
13·60	12·82	—	—	—	—	25·1	18·6	—	(1)
10·38	9·79	22·49	13·66	—	—	—	—	4	
5·28	6·55	16·93	12·85	—	—	28·63	19·25	9	
4·38	5·46	—	—	34·19	22·34	29·55	19·30	9·5	(2)
4·32	5·28	13·38	10·33	—	—	—	—	2·5	
4·10	5·22	20·23	14·12	—	—	—	—	8	
2·94	4·03	13·19	9·86	—	—	—	—	7	
2·88	3·96	—	—	30·39	23·79	—	—	7	(3)
2·73	3·82	17·12	11·92	—	—	—	—	7	
2·68	3·73	13·90	10·05	—	—	—	—	7	
2·40	3·42	—	—	35·93	20·26	29·41	16·58	7	(4)
2·09	3·09	18·99	12·74	—	—	—	—	7	
1·78	2·76	19·19	12·04	—	—	—	—	9	(5)
1·55	2·54	16·40	14·10	—	—	—	—	23	(6)
1·29	2·11	14·76	9·90	—	—	—	—	7	(7)
1·26	1·87	12·65	8·54	—	—	—	—	8 (days)	(7)
1·24	2·11	25·59	15·05	36·48	21·12	30·24	17·51	32	(8)
1·16	1·95	18·54	12·05	—	—	—	—	8	
0·928	1·67	13·69	8·85	35·02	20·39	28·53	16·63	7	(9)
0·934	1·61	—	—	—	—	30·64	18·28	5	(10)
0·681	1·24	13·43	8·34	—	—	—	—	10	
0·680	1·24	15·39	9·36	—	—	29·74	16·42	13	(11)
0·502	1·00	—	—	—	—	30·12	17·85	12	(12)
0·212	0·436	17·20	9·89	—	—	28·49	15·79	9	(13)
0·102	0·209	15·95	8·74	—	—	—	—	—	(14)
0·0418	0·091	11·71	6·44	—	—	—	—	6	
0·037	0·084	10·69	5·88	—	—	—	—	3·5	
0·0354	0·0807	13·91	7·47	—	—	—	—	6	
0·0248	0·055	9·77	5·12	—	—	23·48	12·17	9	(15)
0·0143	0·033	16·82	8·31	—	—	—	—	11 (days)	(16)
0·0133	0·0308	—	—	—	—	23·25	11·86	3 (days)	
0·0103	0·021	8·88	4·45	—	—	18·29	9·17	5	(17)

Notes to Table III.—(1) This was a special experiment made in an attempt to obtain a pair of points in the very concentrated region of the two-liquid system. A very viscous concentrated basic solution was prepared by method (iii). After filtration it was evaporated at room temperature over calcium

chloride and gave a brittle glass (containing 30·24% Al_2O_3; 24·76% SO_3). This was then equilibrated over another basic solution which it was thought might be related to the glass as the complementary liquid phase. The glass increased in weight by nearly 24% owing to water absorption during the first 12 days. A decrease in weight then began owing to devitrification of the glass, with formation of crystals of $5Al_2O_3,6SO_3,46H_2O$. The rate of decrease in weight gradually diminished and a plot of the weights at different times showed that a constant weight of 0·44 g. would have been reached after 120 days from the start of the experiment which, however, was stopped for analysis after 89 days when the weight was 0·4413 g. The composition of the equilibrated solid (referred to the 120-days final weight) was 26·26% Al_2O_3; 21·63% SO_3. It was an opaque hard lump, all the original pieces of glass having joined together. Examination with a lens during the solution in 2N-hydrochloric acid showed it to consist of small, but well-formed, prisms of $5Al_2O_3,6SO_3,46H_2O$ cemented together by (presumably) glassy material. During the course of the equilibration many crystals of $5Al_2O_3,6SO_3,46H_2O$ had also separated from the liquid solution. The latter was filtered from these and the composition found by analysis is given in Table III.

A line drawn from the $5Al_2O_3,6SO_3,46H_2O$ point on the triangular diagram through the point corresponding to the equilibrated solid was produced until it cut the curve drawn through the points for the solutions in Table III. This gave 25·1% Al_2O_3; 18·6% SO_3 as the probable composition of the " glass " in equilibrium with the solution containing 13·6% Al_2O_3; 12·82% SO_3.

(2) The mixture for this experiment was prepared by adding the air-dried precipitate obtained by three-fold dilution of a concentrated solution to some of the undiluted solution. The " glassy " solid, analysed after 9·5 weeks' shaking at 25°, had almost the *R* value to be expected (according to the majority of the results in Table III) for one in equilibrium with the concentrated solution and not with one a third of the concentration. The composition of the original glassy solid must have been adjusted during the shaking, which was possible because the particles were very fine. In this particular experiment equilibration was done at room temperature, which is the probable reason for the water content of the equilibrated solid being considerably higher than it should have been.

(3) Solid phase was a mixture of " glassy " solid and $5Al_2O_3,6SO_3,46H_2O$. The solution point falls exactly on the curve of the two-liquid system.

(4) This mixture was prepared by method (iii) and filtered, and the clear solution heated in boiling water for 6 hours, water lost by evaporation being replaced. Much glassy solid separated. This was allowed to settle, and half the solution removed by decantation. The rest of the solution and the solid were then shaken at 25° for 7 weeks. The solution and the equilibrated solid point fall on the curve of the two-liquid system, but the solid is considerably more basic than corresponds to the majority of the experiments in Table III. It was a mixture of fair-sized glassy discs and finer material, and its amorphous nature was confirmed by *X*-ray examination.

(5) The mixture of this experiment had been prepared without much heating by method (iii) to contain approx. 2·69% Al_2O_3, 3·25% SO_3. It was inoculated with a very small amount of crystals of both $5Al_2O_3,6SO_3,xH_2O$ and $5Al_2O_3,3SO_3,xH_2O$. After 2 days' shaking at 25° a small amount of solid phase was present which contained a large proportion of needles of $5Al_2O_3,6SO_3,46H_2O$. The rest seemed to consist of the glassy solid, but no crystals of $5Al_2O_3,3SO_3,xH_2O$ could be distinguished.

The mixture was then heated for some time. This destroyed the crystals of $5Al_2O_3,6SO_3,46H_2O$ and caused much glassy solid to separate. The mixture was again inoculated with some of the same two crystalline solids as had been previously used, but these had all dissolved when the mixture was examined after 3 weeks' shaking at 25°. After 9 weeks' shaking at 25° from the second inoculation the (silica) tube was opened and the contents separated for analysis. No crystals of either inoculant could then be detected. Much of the solid was in the form of irregular and disc-like glassy fragments with much finer material. The solution point and tie-line are absolutely typical of the two-liquid system.

The most remarkable feature of this experiment is that the solution which was originally supersaturated with respect to $5Al_2O_3,6SO_3,46H_2O$ became unsaturated with respect to it—temporarily at least—after heating. This indicates some important change in the nature of the aqueous solution caused by heating, as does the change in viscosity referred to on p. 2260.

(6) The solid phase was a mixture of prisms of $5Al_2O_3,6SO_3,46H_2O$ with a considerable proportion of relatively large discs of glassy solid. The aqueous solution was still somewhat supersaturated in all probability (see p. 2249). After only 9 weeks' shaking at 25° it had contained Al_2O_3, 1·85; SO_3, 2·76%. The refractive index of the " glassy " discs was $1·477 \pm 0·003$ (see p. 2258).

(7) The solution points for these two experiments fall on the curve of the two-liquid system I and give almost identical tie-lines. The mixture for the experiment giving a solution of *ca.* Al_2O_3, 1·29; SO_3, 2·11% was prepared by method (iii) followed by dilution, while the mixture for the other experiment was obtained by boiling 0·5 g. of $5Al_2O_3,6SO_3,xH_2O$ with 10 c.c. of water for an hour. This second solution was still slightly supersaturated owing to the short period of shaking.

(8) The solution had exactly the same composition after only 16 weeks' shaking. The solid was glassy, in characteristic bright groups of spherical particles. The points for solution and for moist and equilibrated solids fall exactly on a straight line. The *X*-ray diagram showed that, while the solid was essentially amorphous, there was a very small admixture of the crystalline $5Al_2O_3,3SO_3,xH_2O$. This experiment is also quoted in Table V.

(9) This mixture had been prepared from 4·49 g. of aluminium and 500 c.c. of 0·515N-sulphuric acid warmed to 30° for 3 days; reaction was then complete, much glassy solid having separated. Mercury globules were separated by decantation, and the mixture left in a tightly corked flask at room temperature for 68 months, after which period the " solid " still consisted entirely of glassy material. Some of the mixture was then shaken at 25° for 7 weeks, and solution and moist solid were then separated and analysed with the results shown. These give a tie-line which is perfectly normal in comparison with those given by the other experiments of Table III. It cuts the curve of the two-liquid system at a point corresponding to Al_2O_3, 30·60; SO_3, 18·25%, which should be the composition of the equilibrated glassy solid.

The rest of the mixture was filtered on the pump, and the solid washed with 50 c.c. of cold water and

air-dried (yield 8·6 g.). It was greyish owing to the presence of 0·8% of finely divided mercury. Analytical results quoted have been corrected for this. The composition of the solid before and after equilibration over the 25° equilibrium solution is shown in Table III. Its somewhat different composition and greater basicity as compared with that indicated by the tie-line passing through the point corresponding to the moist solid is probably due mainly to the fact that the 8·6 g. of filtered solid had been in equilibrium with solution, not at 25°, but at an average temperature which was about 10° lower.

This experiment illustrates the remarkable persistence of the metastable " glassy " condition.

(10) This had been allowed to stand for 6 weeks at room temperature after preparation, and was then shaken for 5 weeks at 25°. The solid was shown to be amorphous by *X*-rays.

(11) The equilibrated solid is slightly too basic and so is not quite in line with the solution and moist solid points.

(12) This solid was in the form of fairly large glassy spheres, shown to be amorphous by *X*-rays, which had been formed by the gradual dilution of a much more concentrated solution over a period of about 2 months. It is rather less basic than it should be to fall into line with most of the experiments in Table III, owing probably to the inner portions of the spheres having separated from more concentrated solutions which were in equilibrium with more acidic glasses than the more dilute solutions.

(13) This mixture was prepared by method (iii), followed by tenfold dilution. The solid phase was shown to be amorphous by *X*-rays.

(14) This mixture had been prepared from 1·35 g. of aluminium and 500 c.c. of 0·103N-sulphuric acid warmed to 30° for 3 days; reaction was then complete, much glassy solid having separated. Mercury globules were separated by decantation, and the mixture was kept at room temperature, in a tightly corked flask, for 68 months. The solid phase was then seen to consist mainly of glassy solid with a small proportion of fairly large crystals. These were in the form of somewhat rounded St. Andrew's crosses seen, in polarised light, to be due to twinning or intergrowth of prisms. A portion of the mixture was shaken at 25° for 2 months, and solution and moist solid then analysed, with the results shown in Table III. The tie-line shows that *R* of the glassy solid was about 1·39. The rest of the mixture was stirred, allowed to settle for a short time, and the coarse crystals separated by decantation. To the settled mixture of crystals with about 5 c.c. of solution were added 5 c.c. of 2N-hydrochloric acid. After about 30 minutes at room temperature all glassy solid had dissolved, but the crystals appeared unaltered. The solution was opalescent from a trace of semi-colloidal mercury, from which the crystals were easily separated by decantation. They were then filtered off, well washed with cold water, and air-dried. The yield of crystals was only 0·0244 g., and they contained Al_2O_3, 45·97%; SO_3, 15·60%; $R = 2·31$, and gave a characteristic *X*-ray diagram. The crystals are those of a new compound $7Al_2O_3,3SO_3,xH_2O$ (see p. 2271). The original decantate from these crystals had been kept, and 3 years later a further very small amount of much smaller crystals was separated from the mixture by repeated settlement and decantation. There was not sufficient for analysis but only for *X*-ray examination. This showed that the crystals consisted of $5Al_2O_3,3SO_3,xH_2O$ after separation and air-drying. This suggests that the solution of this experiment gives a point very close to that at which the solubility curve of $5Al_2O_3,3SO_3,xH_2O$ cuts that of $7Al_2O_3,3SO_3,xH_2O$. The solution point actually found is on the curve of two-liquid system I, and probably very slightly supersaturated towards one or both of these two crystalline basic salts. The recorded results are explicable if the $7Al_2O_3,3SO_3,xH_2O$ first obtained was actually metastable towards $5Al_2O_3,3SO_3,xH_2O$.

It seems likely that the solubility curve of $7Al_2O_3,3SO_3,xH_2O$ will cut that of γ-$Al_2O_3,3H_2O$ (hydrargillite) before cutting that of the two-liquid system I, which is probably metastable towards some crystalline compound over the whole of its range (see Fig. 2).

(15) This mixture was prepared by pouring rapidly into 5 l. of distilled water at 25°, 20 g. of a clear solution containing approximately Al_2O_3, 4·3; SO_3, 5·3%. Solid began to separate after about 10 sec. After settling overnight, most of the clear liquid was decanted, and by repeating the settling process most of the rather bulky solid and about 60 c.c. of solution were transferred to a large silica tube in which it was shaken at 25°. The solid used for the equilibration experiment had been given one small wash with water and air-dried, and was in moderately hard lumps which remained in this condition at the end of the experiment, which took 6·5 weeks.

(16) In each of these experiments 0·11 g. of $5Al_2O_3,6SO_3,xH_2O$ was boiled with 65 c.c. of water in silica flasks for 2 hours. The one mixture after 11 days' shaking at 25° was filtered, and solution and moist solid were analysed. The second mixture was filtered after 3 days' shaking at 25°. The solution was analysed, and the solid washed with a little water, air-dried, equilibrated over some of the solution, and then analysed. The tie-lines are normal for the two-liquid system I. Equilibrium between solid and solution had adjusted itself quickly because of the small amount of solid present. *X*-Ray examination showed the solid to be amorphous.

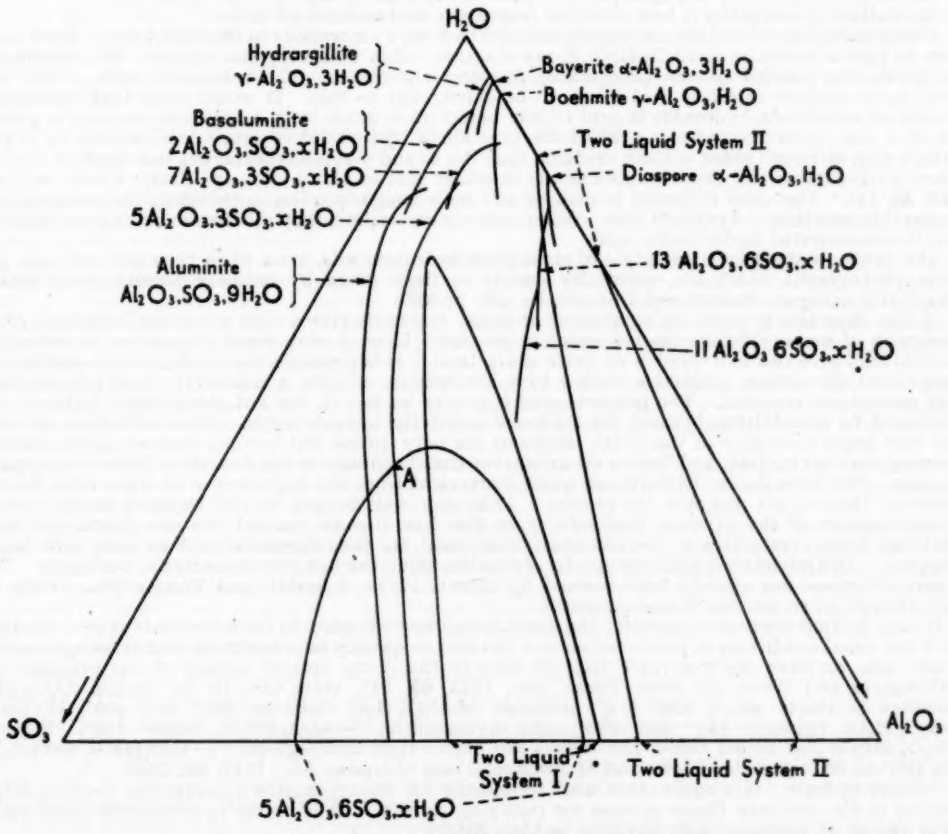
(17) The mixture was prepared and the experiment carried out as in Note (15) by pouring 20 g. of a solution containing approximately Al_2O_3, 4·6; SO_3, 7·2% into 10 l. of water. The equilibrated solid was soft but friable. Equilibration took only 4 weeks.

It was found on numerous occasions that, in the more concentrated region of two-liquid system I, if the basic solutions were heated to about 100° for some time, during or after preparation, their subsequent behaviour was considerably altered. The separation of crystals of $5Al_2O_3,6SO_3,46H_2O$, was hindered, but formation of crystals of the very basic $5Al_2O_3,3SO_3,32H_2O$ (see pp. 2266, 2267) appeared to be facilitated. The heating probably causes the formation of more basic complexes and leads to a complete readjustment of the equilibrium of the solutions which on cooling only slowly returns to that appropriate to the lower temperature. This means that solutions of the same percentage composition may at the same temperature and pressure have different ionic compositions. The case is analogous to that of solutions containing green and purple chromic salts or of solutions containing ortho- and pyro-phosphates. The existence of such differences in the case of basic aluminium sulphates is supported by experiments made at Billingham in 1935 which showed that the viscosity of

basic aluminium sulphate solutions, after 3 hours' heating to 100°, increased by an amount which, though small, was probably significant. It was 6% for a solution containing about Al_2O_3, 10; SO_3, 12%, but only 3% for a less basic one containing about Al_2O_3, 10; SO_3, 15%. A phosphate solution containing much pyrophosphate might similarly be unsaturated towards an orthophosphate to which it would be saturated if all the dissolved phosphate were in the form of orthophosphate.

Any change in the ionic composition of the solution would be reflected in the composition of glassy solid which separated from it. This would account for the results obtained in the experiment in Table III to which Note 5 refers. Other evidence for the effect of heating on the nature of basic aluminium sulphate solutions is considered later (p. 2273).

FIG. 2.



Key to Fig. 2.

Suggested probable relative positions of the solubility curves in the immediate neighbourhood of the water point on a much larger scale than that of Fig. 1. Some idea of the scale can be obtained from the concentrations at point A which are about Al_2O_3, 1·2; SO_3, 2·1%. *If the diagram could be drawn truly to scale all the points where curves cut the right-hand side of the triangle would probably appear within the very short range* 0—0·01% Al_2O_3, *except perhaps the lower point for the curve of two-liquid system II.*

Two-liquid System II.

The curds obtained from aluminium hydroxide sols by the action of sulphate ions and aluminium hydroxide precipitated by ammonia from sulphate solution contain considerable amounts of sulphate which it is almost impossible to remove by washing with water. These facts suggested some relationship to the "glassy" solid phase of the two-liquid system I, as did the general behaviour of hydroxide sols (Bassett and Durrant, *loc. cit.*, p. 280). Investigation of the matter appears to show that these hydroxide curds and precipitates represent the more concentrated phase of a second two-liquid system more basic than that already considered.

It is surprising how difficult it is to obtain an aluminium hydroxide precipitate which is truly amorphous to *X*-rays. This can only be done, in our experience, by precipitation in the cold with the minimum amount of alkali; we always used ammonia. Even when so obtained, most aluminium hydroxide precipitates, after being washed and dried at room temperature, give an *X*-ray diagram containing a few broad lines corresponding to the chief lines of boehmite or γ-Al_2O_3,H_2O. In many cases these are sharp enough to be referred to sub-crystalline (*i.e.*, particles of diameter 500—600 A.)

rather than amorphous (*i.e.*, less than 50 A.) material. In other cases, superimposed on this sub-crystalline boehmite pattern, are the two innermost lines of the bayerite (α-$Al_2O_3,3H_2O$) diagram. As a rule these are so sharp as to indicate the presence of truly crystalline rather than sub-crystalline material. As the proportion of this present in the specimen increases, the number of sharp lines due to bayerite also increases. This is important, as the two innermost lines of the bayerite (α-$Al_2O_3,3H_2O$) diagram are indistinguishable from the corresponding lines of γ-$Al_2O_3,3H_2O$. It is evident that the normal change is from sub-crystalline boehmite (γ-Al_2O_3,H_2O) to crystalline bayerite (α-$Al_2O_3,3H_2O$).

Precipitation in the cold with a large excess of ammonia favours the formation of α-$Al_2O_3,3H_2O$ with particles large enough to yield a very sharp *X*-ray pattern. Aluminium hydroxide precipitates obtained with ammonia seldom give *X*-ray diagrams indicative of the presence of amorphous or sub-crystalline hydrargillite (γ-$Al_2O_3,3H_2O$) but occasionally such precipitates are obtained.

Crystalline hydrargillite is best obtained from sodium aluminate solutions.

Precipitates formed at 100° are translucent and look very amorphous to the naked eye. They alway seem to give a boehmite (γ-Al_2O_3,H_2O) *X*-ray diagram, often with very sharp lines. This shows that the crystalline portion of the precipitatee is relatively coarse. The reluctance with which such precipitates dissolve in dilute acid seems to be chiefly due to this. It would seem that real ease of solution of aluminium hydroxide in acid is only found when much truly amorphous material is present and that the reactivity towards acid of the crystalline hydroxides is determined largely by crystal particle size, although there is some evidence that the α- and γ-monohydrates are less reactive that the α- and γ-trihydrates and dissolve more slowly in either acid or alkali (see, *e.g.*, Frary, *Chem. and Ind.*, 1946, **65**, 14). The chief difficulty in making any such comparison lies in obtaining the compounds in comparable conditions of particle size. When coarsely crystalline, they all dissolve with great difficulty even in concentrated hydrochloric acid.

The curds obtained by coagulation of aluminium hydroxide sols, even when they are very old, give *X*-ray photographs which are essentially similar to those given by ordinary aluminium hydroxide precipitates (compare Bassett and Durrant, *loc. cit.*, p. 289).

X-Ray diagrams of partially amorphous or glassy materials give a very uncertain indication of the proportion of non-crystalline matter which is present. Even a very small proportion of crystalline material may give rise to a number of quite sharp lines. It is probable that both the cold- and the hot-precipitated aluminium hydroxide, which look amorphous, contain a relatively large proportion of truly amorphous material. The proportion of this may be less in the hot-precipitated material, and this would be an additional reason for its lower reactivity towards acids. The boehmite lines when they first begin to appear in the *X*-ray diagrams are very diffuse but become sharper as the material becomes more crystalline, and this is an indication that boehmite is the first crystalline compound to separate. The lines due to bayerite are quite sharp right from the beginning even when only the two innermost lines of its diagram are present. This may well be due to the bayerite resulting from recrystallisation of the primary boehmite when this has already reached the sub-crystalline stage. Relatively large crystallites of the secondary compound are thus formed almost as soon as it begins to appear. The initial slow building up of a crystalline structure has been doen by the boehmite. This curious difference has already been noticed by Kraut, Flake, Schmidt, and Volmer (*Ber.*, 1942, **75**, 1357) though no reason for it was suggested.

It may be that diaspore is actually the first crystalline hydroxide to form, but that it is so unstable under the usual conditions of precipitation and changes so quickly into boehmite that it escapes notice. In any case we have never noticed diaspore lines in the *X*-ray spectra of any of our preparations. Laubengayer and Weisz (*J. Amer. Chem. Soc.*, 1943, **65**, 247) state that in the system Al_2O_3–H_2O corundum is stable above 450° ± 5°, diaspore (α-Al_2O_3,H_2O) between 280° and 450°, boehmite (γ-Al_2O_3,H_2O) between 155° and 280°, and hydrargillite (γ-$Al_2O_3,3H_2O$) below 155°. Bayerite (α-$Al_2O_3,3H_2O$) also occurs below 155° but is less stable than hydrargillite. γ-Alumina is metastable from 100° to 500° (see also Cooke and Haresnape, *Trans. Faraday Soc.*, 1947, **43**, 395).

" Bayer hydrate " is a name often used technically for the crystalline hydrargillite (γ-$Al_2O_3,3H_2O$) obtained in the ordinary Bayer process for purifying bauxite. It is better to avoid this name owing to the danger of confusion with bayerite (α-$Al_2O_3,3H_2O$).

TABLE IV.

Two-liquid system II at 25°.

Solution.		Equilibrated curd.			*n* value of curd (Bassett & Durrant, *loc. cit.*).*		
Al_2O_3, %.	SO_3, %.	Al_2O_3, %.	SO_3, %.			Expt.	Note.
0·0012	0·0017	30·12	8·82	Aluminium hydroxide precipitated by ammonia from sulphate	7·0	(*a*)	(1)
0·0006	0·0016	42·53	8·19		11·2	(*b*)	
Too little to detect		13·62	2·34		12·7	(*c*)	
,,	,,	8·13	1·36		13·1	(*d*)	
0·0011	0·0025	34·96	5·67	Curd precipitated from aluminium hydroxide sols. by $(NH_4)_2SO_4$	13·5	(*e*)	(2)
0·0005	0·0016	48·83	4·77		23·0	(*f*)	
0·0002	0·0005	44·98	3·32		30·9	(*g*)	
Too little to detect	0·02	38·23	2·66		32·8	(*h*)	

* n = equivs. of $Al(OH)_3$/equivs. of bound Al''', where bound Al''' is equivalent to the SO_4'' present (Bassett and Durrant, *loc. cit.*, p. 281).

Notes to Table IV.—(1) 2 G. of $Al_2(SO_4)_3,16H_2O$ were dissolved in 20, 60, 600, and 2000 c.c. of water, corresponding to experiments (*d*), (*c*), (*b*), (*a*) in Table IV, and each solution was treated in the cold with 6 c.c. of 3·2N-ammonia. Precipitates were well washed with cold water till they gave no reaction with Nessler's reagent, and then shaken with 20 c.c. of water in silica tubes at 25° for 6—8 weeks; the mixtures were then separated for analysis of the solutions and precipitates. The latter were washed with a few c.c. of water, air-dried for 48 hours, and then equilibrated over some of the corresponding solution before analysis. Equilibration took about 7 weeks. The more dilute the solution from which the precipitate had been originally formed, the larger the proportion of sulphate present in the precipitate.

The *X*-ray diagram of hydroxide (*a*) showed only the haloes characteristic of a glass. The hydroxides of experiments (*b*), (*c*), and (*d*) all gave *X*-ray patterns characteristic of incipient boehmite crystallisation and suggestive of the presence of particles with diameters of 50 A. or less.

(2) The procedure in the four aluminium hydroxide sol experiments was essentially similar to that described above except that the precipitates were obtained by the action of ammonium sulphate on the sols. The curds are not very easy to wash. Analyses of sols 7, 9, and 12 and details of their preparation are given by Bassett and Durrant (*loc. cit.*).

(2) Sol 4, when 8 days old, contained the following species in concentrations given in milligram-equivs. per litre:

Total Al.	Un-ionised Al.	Bound Al$^{\cdots}$.	Free Al$^{\cdots}$.	Cl′.	*n*.
1037·6	898	99	40·6	139·6	9·07

It had been prepared from hydroxide precipitated in the cold from $Al_2(SO_4)_3$ solution.

The ages of these sols at the date of the present experiments are shown below in parentheses. Details of each experiment are given below.

(*e*) Sol 9 (3½ yrs.). 80 C.c. of slightly opalescent non-thixotropic sol were pipetted away from a considerable sediment of bayerite (α-$Al_2O_3,3H_2O$) and curded with 0·2 g. of ammonium sulphate in 5 c.c. of water. *X*-Ray examination of the curd showed lines due to sub-crystalline boehmite together with a series of spots due to a small proportion (5% ?) of crystalline material. Comparison with the *X*-ray diagrams of the crystalline basic sulphates and hydrated aluminas showed that this crystalline material was almost certainly the basic sulphate with $R = 2{\cdot}17$.

(*f*) Sol 4 (6½ yrs.). No sediment had separated from this sol, which was translucent and very thixotropic. 35 C.c. were curded with 0·2 g. of ammonium sulphate in 5 c.c. of water. The *X*-ray diagram indicated that the curd contained much sub-crystalline bayerite (α-$Al_2O_3,3H_2O$) plus a little much finer boehmite.

(*g*) Sol 7 (4 yrs.). This was translucent and rather viscous but not thixotropic and had not deposited any sediment. 80 C.c. were curded with 0·2 g. of ammonium sulphate in 5 c.c. of water. *X*-Ray diagram showed this curd to contain sub-crystalline boehmite.

(*h*) Sol 12 (2¾ yrs.). This translucent, very thixotropic sol had deposited no sediment. 55 C.c. were curded with 0·2 g. of ammonium sulphate in 5 c.c. of water. According to the *X*-ray diagram this curd contained sub-crystalline boehmite. The solution in this experiment was found to contain an excessive amount of sulphate (0·02%) but insufficient Al_2O_3 to be detected. The solution gave a strong reaction with Nessler reagent, so it is evident that in this case the curd had not been sufficiently washed. The results have been included in Table IV because they seem to fall into line with the others in spite of the presence of this ammonium sulphate.

There is still lack of agreement as to which forms are to be designated α- and γ-, and γ-forms are nowadays sometimes called β-forms, so it is best always to give the mineralogical name in addition to any alphabetical prefix. α-$Al_2O_3,3H_2O$ has not been found as a mineral but the name bayerite is often applied to it. The synthetic γ-Al_2O_3,H_2O is now generally called boehmite, bauxite being regarded as the name of a "rock" which, though often consisting mainly of γ-Al_2O_3,H_2O, may contain other hydrates of alumina and other constituents too.

The more basic two-liquid system was studied as described in the notes attached to Table IV, which summarises the results obtained.

The four experiments with precipitated aluminium hydroxide recorded in Table IV give a smooth curve as shown in Fig. 1 which is very similar to that given by the more acid two-liquid system I. The four experiments with curds from aluminium hydroxide sols give points displaced from this curve in the direction of the Al_2O_3 point. This may well be due to the proportion of crystalline or sub-crystalline material present in these curds, and from 25 to 33% of such material would be adequate to account for the displacement. The *X*-ray diagrams suggest that an amount of that order must be present. The initial amorphous precipitate of so-called aluminium hydroxide appears to behave as a liquid phase. It may contain $Al(OH)_3$ and AlO·OH molecules and aggregates of these, together with various basic aluminium kations and SO_4 ions. The AlO·OH is the first hydroxide to crystallise, but once the more stable crystals of $Al(OH)_3$ begin to form they grow more rapidly and larger crystals of α- or γ-$Al_2O_3,3H_2O$ appear to be normally obtained at 25° than of γ-Al_2O_3,H_2O. It cannot be supposed that either the crystalline or sub-crystalline hydroxides could dissolve sulphate in the same way as the amorphous "hydroxide" (*i.e.*, the liquid phase), but it is possible that considerable surface adsorption of sulphate and water by the crystalline and sub-crystalline hydroxide would occur. It is the resultants of these three effects due to amorphous, sub-crystalline, and crystalline material which lead to the figures shown in Table IV.

The view that amorphous precipitated aluminium hydroxide is a second, very concentrated liquid phase in equilibrium with a very dilute aqueous solution gives a reasonable explanation of the facts, and explains its peculiar properties, in particular, its capacity for "carrying down" and obstinately retaining other constituents of the solution. It is probable that many other amorphous precipitates have a similar nature. The curve of this second two-liquid system probably runs from a point on the

H_2O–Al_2O_3 side of the triangular diagram very close to the H_2O point and eventually returns to the same side of the triangular diagram at a point rather further from the H_2O point. These two points correspond to the aqueous solution free from sulphate and to the pure amorphous liquid hydroxide phase, also free from sulphate, with which it is in equilibrium. This two-liquid system will be metastable towards the crystalline hydroxides—hydrargillite (γ-$Al_2O_3,3H_2O$), bayerite (α-$Al_2O_3,3H_2O$), and boehmite (γ-Al_2O_3,H_2O)—and to the crystalline basic aluminium sulphates. Hydrargillite alone of the crystalline hydrated aluminas has a stable range of existence at 25° in contact with extremely dilute solutions in the immediate neighbourhood of the water point.

The composition of the aqueous solutions in Table IV is subject to considerable uncertainty owing to the very low concentrations and the minute weights of alumina and barium sulphate obtained in the analyses.

The values of n for the hydroxide phase of two-liquid systems II are shown in Table IV, where n is defined. Fig. 1 shows that the lowest n value corresponding to any point on the curve of two-liquid system II is about 7, and for the greater part of the curve the value does not rise above 13. It is evident that near where the curve cuts the H_2O–Al_2O_3 side of the triangular diagram the hydroxide phase may have very large n values (up to infinity !). It may be that the two-liquid system curve obtained with completely amorphous aluminium hydroxide would lie a little more to the SO_3 side of the diagram and correspond to a minimum n value of 6. It seems possible that no aluminium hydroxide sol can have micelles with a smaller n value than 6. This would correspond to complete conversion of the hydroxide into $7Al_2O_3,3SO_3,xH_2O$, the most basic sulphate for which there is any evidence. Bassett and Durrant's method (*loc. cit.*) does not enable the minimum value of n to be determined with any certainty owing to complications caused by the presence of basic kations in the aqueous solution as well as in the micelles.

The bivalent sulphate ion is not a satisfactory anion for positive aluminium hydroxide sols. Such sols would usually break up into the two-liquid system aqueous solution–curd. It may be presumed that any such sols, which are obtainable, will be represented by points which fall within the closed curve of two-liquid system II.

The *X*-ray diagrams of the " glassy " or amorphous phases of two-liquid systems I and II both show very faint indications of broad lines or haloes but are so similar as to be indistinguishable. The glass of two-liquid system I seems to be more stable than the amorphous phase of two-liquid system II but in course of time both begin to show lines in their *X*-ray diagrams which are clearly referable to definite crystalline compounds. In the case of two-liquid system II it is only exceptionally that the amorphous phase does not show from the start lines which are clearly due to incipient boehmite. Boehmite lines never appear in the *X*-ray diagrams of the glassy solid of two-liquid system I. Such lines as do eventually appear suggest incipient formation of either $5Al_2O_3,6SO_3,xH_2O$ or $5Al_2O_3,3SO_3,xH_2O$.

At Black Spring, Doughty Springs, Delta Co., Colorado, a precipitate has resulted from the mixing of an alkaline water with one containing aluminium sulphate. The " mineral " so formed has been called doughtyite [Headden, *Proc. Colorado Sci. Soc.*, 1905, **8**, 66; *J.*, 1906, **90** (Abs.), II, 37]. We have taken the *X*-ray diagram of the British Museum Specimen (B.M.1910.475) and find it to be typical of an amorphous material and just like that of the fully amorphous phases of two-liquid systems I and II. The specimen was collected by Headden at the same time as the sample he analysed. The strongest line of the quartz diagram—somewhat " spotty "—is seen, thus indicating the presence of a few fine grains of quartz in the specimen. Headden's analytical results correspond with those required by the formula $Al_2(SO_4)_3,5Al_2(OH)_6,21H_2O$ (40·8% Al_2O_3; 16·0% SO_3). This composition does not give a point on our curve for two-liquid system II—40·8% Al_2O_3 would require only about 10% SO_3 on our curve. It is not known at what temperature the doughtyite had been precipitated, and the material analysed had probably been air-dried for some considerable time. Both these factors would have a great effect on the composition : the solid in Table IV which contained, after equilibration, 30·12% Al_2O_3; 8·82% SO_3, had the much higher content of 41·02% Al_2O_3; 12·02% SO_3 before equilibration. It is suggested that doughtyite in its original condition had contained about 10% Al_2O_3, 4% SO_3, and represented a glassy phase of two-liquid system I. This had lost much water between the times when it was collected and analysed.

Crystalline Compounds covering the R *Range of* 1·67—2·33 (Plate, Nos. 11—14).

There are at least five compounds in this range with R values of 1·67, 1·83, 2·00, 2·17, and 2·33 with distinct *X*-ray diagrams.

The compound with $R = 2·00$ has, so far, only been found as a mineral, and the compounds with $R = 1·83$ and 2·17 have only been obtained by the sol method. Both $5Al_2O_3,3SO_3,xH_2O$ and $7Al_2O_3,3SO_3,xH_2O$ have been prepared by method (iii) from solutions containing only Al_2O_3, SO_3, and water. $5Al_2O_3,3SO_3,xH_2O$ can also be prepared by the sol method and, best of all, by a modification of the latter.

The extremely short range of stable (?) existence of these very basic compounds constitutes the major difficulty in their preparation. This range at 25° appears to be between the approximate concentration limits Al_2O_3, 1·2; SO_3, 2·1% and Al_2O_3, 0·0005; SO_3, 0·0015%. At the one end of this range $5Al_2O_3,6SO_3,46H_2O$ becomes the stable (?) solid phase, and at the other end hydrargillite.

It is not possible to say with certainty whether, in the three-component system at 25°, any of these compounds are entirely metastable, nor can it be stated which of them have definite ranges of stability in contact with solution or what the limits of the ranges are. If, however, as suggested on p. 2273, the compounds with $R = 1·83$ and 2·17 have structures based on that of diaspore, they would probably be metastable at 25° towards $5Al_2O_3,3SO_3,xH_2O$ and

$7Al_2O_3,3SO_3,xH_2O$ if these have a layer-lattice structure based on that of boehmite. $5Al_2O_3,3SO_3,xH_2O$ and $7Al_2O_3,3SO_3,xH_2O$ would in their turn be metastable towards basaluminite and aluminite if these have structures related to that of hydrargillite (see Fig. 2).

The sol method enables highly supersaturated solutions to be prepared from which by appropriate procedure the basic salts with $R = 1{\cdot}67$, $1{\cdot}83$, or $2{\cdot}17$ can be obtained in a well-crystallised condition and in reasonable amounts. Separation of amorphous matter causes no difficulty in the preparation of the compounds with $R = 1{\cdot}83$ or $2{\cdot}17$ by the sol method, but such trouble is met with when preparing the compound with $R = 1{\cdot}67$ by this method. It is evident that two-liquid systems analogous to those found in the system Al_2O_3–SO_3–H_2O also occur in the five-component system involved in the sol method of preparation.

It is interesting, and may have some significance, that the R values of all the known aluminium sulphates, other than double salts, can be expressed by the ratio $x/6$, where x can have most of the values from 1 to 14. The compound with $x = 1$ would be $Al_2(HSO_4)_6,xH_2O$. It is doubtful if it has been prepared. Salts with all other values of x up to 14 are dealt with in the present communication excepting those where x is 4, 7, 8, or 9. These are not known at present, but one is tempted to think that they may be found some day and so complete the series.

(1) $2Al_2O_3,SO_3,xH_2O$.—Steinberg (*J. pr. Chem.*, 1844, **32**, 495) gave the name paraluminite and the formula $2Al_2O_3,SO_3,15H_2O$ to a mineral from Halle, Saxony, the type locality for aluminite. This mineral has always been regarded as a doubtful species, and we found that the British Museum specimen (B.M. 54801) which came from Caden, Morbihan, Brittany, gave the *X*-ray diagram of alunite. Recent discoveries in Northamptonshire (see p. 2251) have thrown new light on the matter. A pure white crystalline mineral has been found in considerable amounts in cracks and fissures in the ironstone which has the same R value (2·0) as Steinberg's paraluminite. It occurs in two forms differing in their degree of hydration. The less hydrated form gives the *X*-ray diagram of the material found by the author and by Bannister and Hey associated with aluminite on many specimens of that mineral. The more hydrated form has quite a different *X*-ray diagram when in the wet state, as found, but on keeping it tends to lose water and then gives the *X*-ray diagram of the lower hydrate. It is of some interest that aluminite has not, so far, been found in the Northampton deposits. The author has been able to analyse a specimen of this new mineral (the less hydrated form) through the kindness of Messrs. Bannister and Hey. It was in soft lumps and the values found for two different lumps were :

	I.	II.		I.	II.
Al_2O_3	44·35%	43·93%	$CaCO_3$	0·45%	0·01%
SO_3	15·56%	16·24%	H_2O (diff.)	36·83%	38·29%
SiO_2	2·81%	1·53%			

Fe, Mg, Na, and K were absent unless in minute traces. The silica was present as a silicate which gelatinised readily with hydrochloric acid (there was no quartz present). This silicate was most probably allophane, $Al_2O_3,SiO_2,5H_2O$, which occurs in the Northamptonshire ironstone mines. Calculating the silica to allophane one gets for the mineral composition :

		I.	II.
Allophane		11·81%	6·43%
Calcite		0·45%	0·01%
As basic sulphate	Al_2O_3	39·57%	41·33%
	SO_3	15·56%	16·24%
	H_2O	32·61%	35·99%

The composition of the pure basic sulphate would be :

	I.	II.
Al_2O_3	45·10%	44·18%
SO_3	17·73%	17·36%
H_2O	37·16%	38·46%
	$R = 1{\cdot}996$	1·996

The results correspond to the formulæ : (I) $2Al_2O_3,SO_3,9{\cdot}25H_2O$, and (II) $2Al_2O_3,SO_3,9{\cdot}88H_2O$, which require (I) Al_2O_3, 45·28; SO_3, 17·76; H_2O, 36·96%, and (II) Al_2O_3, 44·17; SO_3, 17·33; H_2O, 38·50%. The more hydrated form of the mineral contains far more water than is required by the formula $2Al_2O_3,SO_3,15H_2O$. It has been established therefore that there is a mineral having $R = 2{\cdot}0$, but the precise relationship of the two different hydrates of this mineral to Steinberg's paraluminite remains obscure.

The new mineral $2Al_2O_3,SO_3,xH_2O$ (where x is probably 10) has been given the name " basaluminite," while the much more hydrated form has been called " hydrobasaluminite " (Bannister and Hollingworth, *loc. cit.*).

The story of this mineral illustrates the difficulty of attempting to identify minerals of the

nature of the basic aluminium sulphates merely from the appearance or from their locality and mode of occurrence. It would seem that all basic aluminium sulphate minerals require a thorough overhaul, *X*-ray and analytical.

(2) $5Al_2O_3,3SO_3,xH_2O$.—Crystals of $5Al_2O_3,3SO_3,xH_2O$ will separate spontaneously from suitable dilute solutions which have been only moderately heated during preparation by method (iii), but they can also be obtained at 25°, either spontaneously or after inoculation, from more concentrated solutions if these have been heated to from 80° to 100° for some time before being shaken at 25°. Such heating delays separation of $5Al_2O_3,6SO_3,46H_2O$, but does not appear to be necessary in the way that it is when preparation by the sol method is employed (see p. 2267).

The crystals are either small rectangular plates, sometimes with numerous facets, showing straight extinction, or four-sided platelets with angles of 80° and 100°, generally in characteristic doublets, the plates being joined at the acute angles. These doublets extinguish at 40° to one of the sides. Sometimes separate prisms with this extinction angle occur. The two types of crystal appear to be different habits of the same crystal form. A third variant is often obtained when the salt crystallises from solution on the sides of the containing vessel. It is in the form of a wedge looking almost like a right-angled isosceles triangle, the hypotenuse being the thin edge of the wedge and extinction parallel to this.

Solubility data relating to $5Al_2O_3,3SO_3,xH_2O$ at 25° are given in Table V. All the mixtures there recorded were prepared by method (iii).

TABLE V.

$5Al_2O_3,3SO_3,xH_2O$ *at* 25°.

Solution.		Moist solid.		Dry solid.		Equil. solid.		Shaken at 25° for	*R* of	
Al_2O_3, %.	SO_3, %.	Al_2O_3, %.	SO_3, %.	Al_2O_3, %.	SO_3, %.	Al_2SO_3, %.	SO_3. %.	(weeks).	solid.	Note.
9·03	9·33	25·03	15·02	—	—	—	—	4	—	(1)
7·71	8·58	17·72	13·04	—	—	—	—	3	—	(2)
6·98	9·18	24·88	14·55	—	—	—	—	7	—	(3)
7·01	8·44	—	—	37·67	18·44	—	—	1	1·60	(3*a*)
6·87	7·75	25·33	16·04	—	—	—	—	2·5	—	(1)
6·59	6·85	24·10	13·38	—	—	—	—	12 (days)	—	(4)
5·66	7·07	—	—	35·37	18·81	35·17	18·70	12	1·47	(5)
5·46	6·59	—	—	38·24	19·07	35·63	17·77	4·5	1·57	(6)
4·73	6·17	—	—	35·32	20·37	31·94	18·42	8	1·36	(6)
4·00	5·27	—	—	35·73	19·50	33·22	18·12	9·5	1·44	(7)
2·15	3·21	—	—	35·25	19·55	{30·88 29·68	{17·13 16·48}	14	1·41	(8)
1·76	2·74	—	—	38·49	19·05	36·58	18·10	5·5	1·58	(9)
1·24	2·11	25·59	15·05	36·48	21·12	30·24	17·51	32	1·36	(10)
1·25	2·10	—	—	38·42	18·36	36·30	17·35	6	1·64	(11)
0·418	0·808	—	—	34·49	20·03	—	—	9	1·35}	(12)
0·421	0·822	—	—	36·84	18·04	—	—	15	1·60}	

Notes to Table V.—(1) Solid seen under microscope to consist of a mixture of prisms of $5Al_2O_3,6SO_3,46H_2O$ and the characteristic double platelets of $5Al_2O_3,3SO_3,xH_2O$. The mixture had been inoculated with the latter. No glassy solid could be seen, though some had separated at the start of the experiment.

(2) Mixture had been heated to 80° for an hour before being shaken at 25° to destroy prisms of $5Al_2O_3,6SO_3,46H_2O$. Solid phase consisted of a mixture of glassy solid and of well-formed small rectangular (nearly square) crystals showing straight extinction.

(3) Mixture had been heated in boiling water for an hour, which caused glassy solid to separate. After the shaking at 25° all of this had gone and there were only a few fairly large double platelets which were analysed in the moist condition. The tie-line runs very close to the point for $5Al_2O_3,3SO_3,32H_2O$, and nearly as close to that for $5Al_2O_3,3SO_3,35H_2O$. The solution point appears to lie on the true solubility curve of $5Al_2O_3,3SO_3,xH_2O$, which is very metastable in this region towards $5Al_2O_3,6SO_3,46H_2O$.

(3*a*) Solution of aluminium effected quickly by heating, and completed by standing overnight; inoculated with $5Al_2O_3,3SO_3,xH_2O$; after 7 weeks' shaking at 25° crystals of latter had separated, but after further 3 weeks needles of $5Al_2O_3,6SO_3,46H_2O$ were coming out. The bottle was opened and heated in boiling water for 10 minutes to destroy these. After a further 2 days at 25°, only $5Al_2O_3,3SO_3,xH_2O$ and probably a little glassy solid could be seen. The mixture was filtered for analysis. As water caused immediate separation of solid from the mother-liquor, the crystals were first washed rapidly with a few c.c. of 0·4N-hydrochloric acid, then with water, and air-dried. The *X*-ray diagram was typical of $5Al_2O_3,3SO_3,xH_2O$ with probably a very little glassy solid. The solution point lies either on or only just off the curve of two-liquid system I.

(4) The solid consisted mainly of small square plates, and the tie-line runs to a point close to that for $5Al_2O_3,3SO_3,32H_2O$. The solution is considerably supersaturated, and the solid probably contained some glassy solid.

(5) The solid was largely crystalline, apparently very minute square crystals, but the *X*-ray diagram shows that much glass was present also.

(6) The mixture was heated in boiling water for 7 hours, which caused much glassy solid to separate. Nearly all of this had redissolved after 15 hours' shaking at 25°. When the experiment was stopped, the solid consisted largely of the small square crystals, but there was some glass as well.

(7) The solid consisted chiefly of the double platelets of $5Al_2O_3,3SO_3,xH_2O$. No glassy solid could be seen, but the *X*-ray diagram indicates the presence of a considerable amount.

(8) This mixture had been heated considerably, which caused much glass to separate initially. After the long shaking at 25°, the fine solid which must have been mainly glassy contained many small but well-formed double platelets which were large enough for optical measurements. The equilibration curve of this solid showed two breaks, giving the two compositions for the equilibrated solid shown in Table V; water adsorption by the glassy solid continues after that by the partially dehydrated crystals has ceased.

(9) The mixture had been heated to the boil for a long time. The solid analysed was seen to be a mixture of glassy solid and well-formed square plates, showing straight extinction, of $5Al_2O_3,3SO_3,xH_2O$.

(10) The mixture was heated very little during preparation, and not above 25° subsequently. The composition of the solution was exactly the same after 16 weeks' shaking at 25° as after 32 weeks'. The *X*-ray diagram showed that the solid was mainly glassy, but most of the strong lines of $5Al_2O_3,3SO_3,xH_2O$ were showing up. This experiment is also quoted in Table III.

(11) The mixture was only gently heated during preparation, and was filtered before the 6 weeks' shaking from small amount of white solid which had separated during preparation. The solid analysed consisted of small nodular groups of crystals, some of which showed the double platelet form with angles of 100° and 80°. The microscopic appearance showed plainly that the solid was essentially crystalline, but a few thin discs of the glassy solid would have been undetectable among the crystals in the aggregates. The composition of the air-dry solid corresponds very closely to a mixture of 95% of $5Al_2O_3,3SO_3,32H_2O$ with 5% of an air-dry glassy solid of the same composition as that separated from the solution in Table V to which note 10 relates, while the composition of the equilibrated solid corresponds to a mixture of 95% of $5Al_2O_3,3SO_3,35H_2O$ with 5% of the corresponding equilibrated glass. This result is important as indicating that it is the 35-hydrate rather than the 32-hydrate which is in equilibrium with solutions at 25°. The tie-line evidence is so scanty that it cannot decide the precise nature of the solid phases in this part of the diagram.

(12) The mixture for this experiment had not been heated much but it had been inoculated with a little of the square crystals of $5Al_2O_3,3SO_3,xH_2O$. After 9 weeks' shaking the mixture was filtered and analysed; *R* of the solid phase was 1·35, and microscopically it consisted mainly of the glassy solid with a small amount of the square crystals. The solution point falls on the curve of the two-liquid system I. The rest of the filtered solution, after being kept at room temperature for 2½ years in a stoppered bottle, had given a small deposit consisting mainly of fair-sized prisms, extinguishing at 40° to the length when lying flat on the slide, together with a small proportion of characteristic clusters of the discs of glassy solid. This solid together with about half of the mother-liquor was transferred to a small solubility bottle and shaken at 25° for 15 weeks, and solution and solid were then analysed. The solid now seemed to consist only of the prisms; no glass could be distinguished under the microscope, having apparently dissolved with the rise of temperature to 25°. There was plenty of solution for analysis and its composition suggests that it no longer corresponds to a point on the two-liquid system I but that it may represent a point on the true solubility curve of $5Al_2O_3,3SO_3,xH_2O$—slightly on the acid side of the curve of the two-liquid system. The total weight of solid was only 3·8 mg. and the whole analysis had to be done on this small amount, so the experimental error may be considerable.

X-Ray diagrams were taken of all the solids in Table V which were separated in the dry state. The presence of some amorphous material was indicated in most cases, especially when *R* was much below 1·67. The lines in the diagrams were always in the same positions and of similar relative intensities.

The results obtained by method of preparation (iii) and summarised in Table V are important because the mixtures contain only Al_2O_3, SO_3, and H_2O and so enable the solubility curve of the salt $5Al_2O_3,3SO_3,xH_2O$ to be located with some degree of exactness. This curve is found to run very close to the curve of two-liquid system I towards which it is stable, but it cuts the curve of $5Al_2O_3,6SO_3,46H_2O$ at about Al_2O_3, 1·24; SO_3, 2·11%, so that in contact with more concentrated solutions than this it is metastable. It is difficult to obtain $5Al_2O_3,3SO_3,xH_2O$ free from $5Al_2O_3,6SO_3,46H_2O$ from such more concentrated solutions since the more acid salt tends to separate more readily and rapidly from solution. The method allows only small amounts of the salt to be obtained in any reasonable purity. This is chiefly owing to the ease with which contamination by the glassy solid of two-liquid system I can occur owing to the proximity of the two solubility curves and to the ease of separation of $5Al_2O_3,6SO_3,46H_2O$ first referred to.

Large amounts of $5Al_2O_3,3SO_3,xH_2O$ can be obtained in fair-sized crystals by the sol method (v) of p. 2240. It is important to heat the sol to about 100° for at least an hour before addition of the ammonium sulphate in order to obtain good yields and to avoid separation of the compounds with $R = 2·17$ or 1·83 or one of the double salts of the latter with ammonium sulphate.

The conditions of preparation by the sol method are much more complex than was realised by Bassett and Durrant. They failed to notice the presence of ammonia in the five preparations with $R = 1·64$ and 1·67 quoted in their paper [*loc. cit.*, expts. (IV), (V), and (VI), p. 292]. The corrected analysis of one of these preparations is given as an example. No. (i) of preparation (VI) contained Al_2O_3, 40·11; SO_3, 18·96; NH_3, 0·92 [= 3·57% $(NH_4)_2SO_4$]. Now [40·11/102]/[18·96/80] = 1·66, but after deducting SO_3 equivalent to the NH_3, the ratio becomes 1·86. These preparations actually consist of a new double salt (referred to as basic double salt I) $(NH_4)_2SO_4(11Al_2O_3,6SO_3,xH_2O)$ which is considered later. Its *X*-ray diagram differs from that of $5Al_2O_3,3SO_3,xH_2O$.

Bassett and Durrant's "Maltese-cross twins" with $R = 1·70$—1·72 really consist of $5Al_2O_3,3SO_3,xH_2O$,

probably contaminated with $7Al_2O_3,3SO_3,xH_2O$, but only very small yields were obtained in their experiments since the solutions had not been heated long enough. Even the yield of 0·68 g. given at the top of p. 293 of their paper is an error. The yields of fine and coarse material in that experiment have been transposed : that of the coarse was only 0·25 g. and that of the fine 0·68 g. The latter has since been shown to be glassy by *X*-rays.

Details of a number of well-crystallised preparations of $5Al_2O_3,3SO_3,xH_2O$ obtained by the sol method are given in Table VI. All these preparations gave *X*-ray diagrams typical of $5Al_2O_3,3SO_3,xH_2O$. The data given for each experiment relate to 10 g. of $AlCl_3,6H_2O$. In each case the ammonia was added to the chloride solution at room temperature with constant stirring. The mixture was then heated, for the time mentioned, to about 100° and then filtered before dilution and addition of ammonium sulphate. Ammonia was absent from all these preparations. Analyses refer to the air-dry solids.

It is clear that even when prepared by the sol method the conditions for separation of amorphous or glassy solid are very similar to those required by $5Al_2O_3,3SO_3,xH_2O$. The two tend to separate together but, as much larger quantities can be prepared by this method and in larger crystals, the latter are readily separated from the bulk of the amorphous material by treatment with dilute hydrochloric acid : good crystals so prepared still give somewhat hazy *X*-ray diagrams, possibly owing to glassy inclusions in the crystals.† It must be emphasised that this glassy solid which separates from the heated sol mixtures is not a gel obtained by curding a sol but is of exactly the same character as the glassy phase of two-liquid system I of the three-component system Al_2O_3–SO_3–H_2O. A true gel is obtained if the sols have not been heated for a sufficient time before addition of the ammonium sulphate. These gels correspond to the amorphous phase of two-liquid system II of the three-component system. In the simple Al_2O_3–SO_3–H_2O system, $5Al_2O_3,3SO_3,xH_2O$ often seems to form from the two-liquid system I which is metastable towards it, but this change is very slow. Much the same appears to happen in the sol method of preparation, but the presence of ammonium chloride accelerates the change. The amorphous solid which so often, but not always, is the first substance to separate in preparations by this method must be regarded as the amorphous or glassy phase of two-liquid system I. In such cases the major portion of $5Al_2O_3,3SO_3,xH_2O$ obtained results from the transformation of this amorphous phase, but quite a lot also separates from the aqueous liquid phase on the sides of the containing vessel in curious wedge-shaped crystals.

TABLE VI.

$5Al_2O_3,3SO_3,xH_2O$ *prepared by the sol method* : 10 *g. of* $AlCl_3,6H_2O$ *used in each experiment.*

3·2N-NH_3, c.c.	Time sol was boiled, mins.	Vol. of sol boiled, c.c.	$(NH_4)_2SO_4$, g.	Total vol., c.c.	Wt. of solid obtained, g.	Actual *R* value found.	Composition of crystals, %. Al_2O_3.	SO_3.	Note.
20	10	40	3	450	1·6	1·59	35·19 33·89	17·34 16·70	(1)
16·9	15	92	2·5	400	0·68 0·252	1·64 1·72	35·72 39·16	17·06 17·85	(2)
22·5	15	42	3	453	0·49	1·69	38·00	17·64	(3)
10	60	60	2	70	0·502	1·74	39·17	17·69	(4)
15	60	65	2	70	0·822	1·73	38·55	17·45	(5)
22·5	60	97	2·5	120	1·95 1·33	1·70 1·63	38·55 37·20	17·82 17·88	(6)
A*22·5	60	42	3	453	3	1·67	37·44	17·62	(7)
32·7	90	110	20	217	3·91 1·10	1·74 1·67	29·74 38·26	13·38 17·97	(8)
25·9	5 days	46	3	57	3·65	1·68	38·62	18·05	(9)
			Calc. for $5Al_2O_3,3SO_3,31H_2O$:				39·00	18·35	
			,, $5Al_2O_3,3SO_3,32H_2O$:				38·47	18·10	
			,, $5Al_2O_3,3SO_3,34H_2O$:				37·45	17·63	
			,, $5Al_2O_3,3SO_3,35H_2O$:				36·96	17·39	

* See p. 2273.

Notes to Table VI.—(1) Separation of solid began 10 minutes after dilution and addition of ammonium sulphate. After 3 weeks, some of finer portion of solid was separated and found to contain Al_2O_3, 35·95; SO_3, 17·58% in the air-dry state; $R = 1·60$. The rest of solid was separated by decantation, and 7 c.c. of 2N-hydrochloric acid were added to the 70 c.c. of solid plus solution to dissolve any amorphous solid. After 10 minutes' shaking the coarse crystals were filtered off and easily washed free from Cl and NH_3 and then air-dried. The *X*-ray diagram was only taken for the coarse crystals and was characteristic of $5Al_2O_3,3SO_3,xH_2O$. The lower values for Al_2O_3 and SO_3 in the table are for coarse crystals equilibrated over some of the mother-liquor at 25°.

100 C.c. of mother-liquor decanted from the crystals had been treated with a further 1 g. of ammonium sulphate, and after 7 months' standing in a covered beaker had shrunk to 35 c.c. A few small clear alum crystals and some small doubly refracting crystals of $5Al_2O_3,3SO_3,xH_2O$ had separated. The alum crystals were removed but, although they looked pure it was found, on dissolving them in warm water, that they contained a fairly large number of inclusions of crystals of $5Al_2O_3,3SO_3,xH_2O$. This supports the view that many of the apparently good crystals of $5Al_2O_3,3SO_3,xH_2O$ may have contained numerous inclusions of the glassy solid.

(2) Expt. (vii) quoted by Bassett and Durrant (*loc. cit.*, pp. 292, 293) but see p. 2267.

† See p. 2271 for a more probable explanation of the poor *X*-ray diagrams.

(3) Behaviour much as in (1). After 5½ weeks, the mother-liquors were removed by decantation, and 50 c.c. of approx. N-hydrochloric acid were added to the residue. This dissolved amorphous material at once and possibly some of the crystals. The latter were filtered off and washed.

(4) Small crystal deposit first seen a week after admixture. After 8 weeks' standing the volume had shrunk to about 50 c.c., and the solid seemed to consist entirely of the Maltese-cross twins. It was then separated and filtered off and washed easily.

(5) This mixture was quite undisturbed during the fortnight's crystallisation. The solid consisted of clear crystals which behaved like aggregates of plates.

(6) The second crop of crystals with $R = 1{\cdot}63$ had separated during 22 weeks' standing at room temperature of the filtrate from the first crop; about 20 c.c. of water had been lost by evaporation. No amorphous material was visible under the microscope in either lot of crystals.

(7) Much solid was present after 3 days and appeared to be amorphous. After 2 days more it began to show double refraction, and after 8 weeks' standing at room temperature with occasional stirring it looked entirely crystalline. The composition of the air-dry solid corresponds exactly to $5Al_2O_3,3SO_3,34H_2O$.

(8) The ammonia caused a permanent precipitate, so 9 c.c. of 2N-hydrochloric acid were stirred in to dissolve it before the heating. Addition of the ammonium sulphate soon caused a precipitate, and in the hope that this would dissolve, the whole mixture was heated to nearly 100° for some time. This seemed to increase precipitation. The precipitate settled rapidly and after washing and air-drying weighed 3·91 g. It was free from ammonia and amorphous to *X*-rays. After 4 days at room temperature the filtrate had deposited a smaller amount of fair-sized clear crystals free from NH_3 which were interpenetrating twins. After separation from the solution and air-drying they gave the *X*-ray diagram of $5Al_2O_3,3SO_3,xH_2O$. They were equilibrated over a solution which contained Al_2O_3, 1·27; SO_3, 2·00%, after the equilibration. Table V shows that such a solution should be in approximate equilibrium with $5Al_2O_3,3SO_3,xH_2O$. The equilibrated crystals contained Al_2O_3, 37·74; SO_3, 17·74%, approximating to $5Al_2O_3,3SO_3,34H_2O$. The experiment shows how very basic the amorphous solids can be which separate from the solutions on heating, and shows also that $5Al_2O_3,3SO_3,xH_2O$ has no tendency to form a double salt with ammonium sulphate in spite of the high concentration of this.

(9) The ammonia added was just that required to form $[Al(OH)_2]^+$. The 5 days' heating was done in a counterpoised silica beaker and the temperature varied between 50° and 100°. Water lost by evaporation was periodically replaced. Addition of ammonium sulphate caused no immediate precipitate, but after standing overnight at room temperature there was a slight prismatic deposit. The mixture was well stirred, and separation of solid seemed complete after 3 days. The solid was easily washed free from chloride and ammonia. The mother-liquor contained 0·85% Al_2O_3. No alum crystals were present. The experiment is important in showing that, after long heating, pure ammonia-free $5Al_2O_3,3SO_3,xH_2O$ can be obtained from very concentrated solutions.

TABLE VII.

$5Al_2O_3,3SO_3,xH_2O$ *prepared at* 70° *and at* 50°.

Solution.		Air-dry solid.			Time of heating,		
Al_2O_3, %.	SO_3, %.	Al_2O_3, %.	SO_3, %.	Temp.	(weeks).	*R*.	Note.
0·82	1·56	39·20	18·44	70°	4	1·68	(1)
0·022	0·049	37·98	16·82	70	6	1·77	(2)
0·494	0·977	37·41	18·32	50	5	1·60	(3)

Notes to Table VII.—(1) 3 G. of a slightly acid preparation of $5Al_2O_3,6SO_3,xH_2O$ (containing 26·6% Al_2O_3; 26·6% SO_3; $R = 0{\cdot}784$) and 50 c.c. of water were put in a 100-c.c. resistance-glass conical flask which was immersed up to the neck in a thermostat at 50°. The flask was then corked and occasionally shaken. After 16 hours' heating the solid had been converted entirely into amorphous pseudomorphs of the original crystals. The appearance of these was unaltered after a week when the temperature of the thermostat was raised to 70°. After 12 hours at this temperature, about half of the solid had become fairly coarsely crystalline and after a fortnight all amorphous material seemed to have disappeared. Heating was continued for another fortnight before separating solution and dry solid for analysis. Some of the clear solution was pipetted into weighing bottles. The rest of the solution with some of the finest solid was decanted and the remainder of the mixture filtered off on a small Buchner funnel and washed with 3·5 c.c. of water and then 3·5 c.c. of absolute alcohol. The weight of air-dry solid was 1·153 g. The solid was fairly coarsely crystalline in rectangular, nearly square, prisms showing straight extinction, with the roughish appearance described on p. 2271. It dissolved fairly easily on warming with 2N-hydrochloric acid and gave one of the best and clearest *X*-ray diagrams of $5Al_2O_3,3SO_3,xH_2O$ which we have obtained.

(2) Approx. 2 g. of a basic solid (*R* approx. 1·7) prepared by the sol method (and consisting apparently mainly of amorphous material with some crystals of $5Al_2O_3,3SO_3,xH_2O$ was placed in a resistance-glass conical flask with 50 c.c. of water. After an hour at 70° the solid had become largely converted into characteristic nodular and prismatic aggregates, and after 3 days about half seemed to be in this form. The remainder was very fine and might possibly have been amorphous. After a further 5½ weeks at 70° the appearance of the solid was essentially the same, so the mixture was filtered for analysis. The *X*-ray diagram was precisely like that of the previous preparation at 70°.

(3) 0·998 G. of the same basic solid (*R* about 1·7) referred to in Note (2) together with 0·803 g. of crystalline $Al_2O_3,2SO_3,11H_2O$ and 25 c.c. of water were heated at 50° in a Hysil-glass flask. After 20 hours' heating the solid was mainly crystalline and appeared to be entirely so after 5 weeks' heating, whereupon the mixture was separated for analysis. It gave a good *X*-ray diagram of $5Al_2O_3,3SO_3,xH_2O$.

Comparison of the figures in Table V and VII shows that, in the case of dilute solutions, the position of the solubility curve of $5Al_2O_3,3SO_3,xH_2O$ hardly changes between 25° and 70°.

The best and clearest crystals of $5Al_2O_3,3SO_3,xH_2O$ are most easily obtained by a modification of the sol method. It involves the initial preparation of a dilute basic aluminium chloride solution of controlled composition and containing no ammonium salts, unlike that prepared by the sol method. This solution is then precipitated by the addition of suitable amounts of ammonium sulphate. The initial basic chloride solution can be prepared by the solution of either aluminium *iso*propoxide or preferably of aluminium in a concentrated solution of aluminium chloride. The following preparations show the method of operation and the results obtained. 10 G. of $AlCl_3,6H_2O$ in about 20 c.c. of water were treated gradually with 17 g. of aluminium *iso*propoxide (containing 25% Al_2O_3). Solution was very slow in the cold but was hastened by boiling, which was continued under reflux for 5 days. This long boiling was given in the hope that it might establish a hydrargillite lattice structure in any " micelles " present in the solution which might facilitate the eventual precipitation of either aluminite or basaluminite should these have structures based on that of hydrargillite (see p. 2273). A small amount of hydroxide had separated from the solution during the boiling and this was filtered off. The clear filtrate was diluted to 500 c.c., and a solution of 5 g. of ammonium sulphate in 50 c.c. of water gradually added. A precipitate began to form after about three-quarters of the sulphate had been added. This appeared to be amorphous. After standing overnight, crystallisation in prisms and rosettes of prisms had begun, and appeared to be complete after 9 days, whereupon the solid was collected on a Buchner funnel and washed with 25 c.c. of cold water which was enough to remove all chloride. Weight of air-dried solid, 3 g., containing Al_2O_3, 38·56; SO_3, 18·00%; $R = 1·68$. The mother-liquor contained Al_2O_3, 0·11; SO_3, 0·49% by weight. The crystals evidently consisted of $5Al_2O_3,3SO_3,32H_2O$, but the important observation was made that during the air-drying of the washed crystals considerable loss of weight continued long after the crystals were dry in the ordinary sense. The crystals were weighed at frequent intervals during 9 days. There was a change in the rate of loss of water which indicated a loss of weight of 3·86% after the ordinary dry stage had been reached which would correspond to a loss of $3H_2O$ from $5Al_2O_3,3SO_3,35H_2O$ (Calc. loss for this change : 3·91%).

A second preparation was carried out in essentially the same way, but the aluminium *iso*propoxide was added more quickly which gave a much more colloidal solution. After the 35 c.c. had been boiled under reflux for 6 days much gelatinous solid had separated. After dilution with 25 c.c. of water the milky mixture gave a clear filtrate after passage through a Whatman No. 41 followed by a No. 42 filter-paper. The filtrate was made up to 100 c.c. and this diluted solution was analysed and found to contain Al_2O_3, 2·56; Cl, 1·93% (w/v). The remaining 95 c.c. of solution were poured into 2600 c.c. of water containing 3·44 g. of ammonium sulphate (the amount equivalent to the chlorine). There was no immediate precipitate but an appreciable amount had formed after 45 hours in the form of minute nearly circular transparent discs or spheres, probably of glassy solid. After 5 days there was much more solid, obviously crystalline in aggregates probably of platy crystals. Separation of solid seemed to be complete after further 3 days, and it was then separated as in the previous preparation. The behaviour of the crystals on drying was the same as in that experiment. Weight of air-dry solid, 2 g., containing: Al_2O_3, 39·46; SO_3, 17·87%; $R = 1·73$. The mother-liquor contained Al_2O_3, 0·04; SO_3, 0·075% by weight. It is thought that the solid was a mixture of 88% of $5Al_2O_3,3SO_3,32H_2O$ with 12% of the more basic $7Al_2O_3,3SO_3,33H_2O$, which requires Al_2O_3, 39·40; SO_3, 17·71%.

In a third preparation 0·9114 g. of aluminium was dissolved in 45·3 c.c. of N-hydrochloric acid by digestion for 5½ hours just below the boiling point, but as solution of the metal was still not complete a globule of mercury was added, and the mixture left overnight over a small flame. The mercury was then filtered off, and the solution poured into a dilute solution of 2·99 g. of ammonium sulphate, the volume of the mixed solution being made up to 2 l. There was no immediate precipitate but a considerable amount after 45 hours' standing. This was found to be relatively coarsely crystalline in separate clear crystals which were fairly thick rectangular plates. These were separated as before and showed the same behaviour on air drying. Weight obtained, 2 g., containing: Al_2O_3, 39·10; SO_3, 17·84%; $R = 1·72$. The mother-liquor contained: Al_2O_3, 0·033; SO_3, 0·068%.

A fourth preparation was carried out in an essentially similar manner from 6·83 g. of aluminium, 536·6 c.c. of N-hydrochloric acid, 35·42 g. of ammonium sulphate, and a final volume of 1 l. A yield of 1·4 g. of air-dry crystals was obtained of composition Al_2O_3, 38·39; SO_3, 17·91%; $R = 1·68$. The composition of the mother-liquor was : Al_2O_3, 1·22; SO_3, 2·07%. This gave a further crop of 1·15 g. of crystals after 5 weeks' standing at room temperature (Found : Al_2O_3, 38·50; SO_3, 18·07%; $R = 1·67$).

Still another solution was made from 0·683 g. of aluminium and 22·65 c.c. of N-hydrochloric acid, and after filtration and dilution to 50 c.c. this was added to a solution of 1·007 g. of ammonium sulphate in 950 c.c. of water. After standing with occasional stirring for a month, solution and solid were separated and analysed. Yield of solid after air drying, 1·9 g. The solution contained Al_2O_3, 0·0266; SO_3, 0·0169%, and the air-dry solid Al_2O_3, 40·77; SO_3, 17·66%; $R = 1·81$. The compositions of the latter corresponds exactly to that of a mixture of 75% of $5Al_2O_3,3SO_3,31H_2O$ and 25% of $7Al_2O_3,3SO_3,33H_2O$.

Since the air-drying had extended over 8 days under conditions of low humidity, the $5Al_2O_3,3SO_3,xH_2O$ may well have lost rather more water than usual. It is to be noted that the most basic " glassy solid " of two-liquid system I of which we have any knowledge had R about 1·74 (see note 8 to Table VI). It is also certain from the microscopic appearances of the present solid and all those prepared in a similar way that it was essentially, if not entirely, crystalline, so that admixture with the $R = 2·33$ salt appears to be the only way of accounting for preparations having $R = 1·7$ or above This applies to preparations made by the usual sol process also. It must be remembered that owing to the presence of ammonium salts the system has more than 3 components. If the NH_4 were equivalent to the Cl, as was approximately the case, the system would be one of 4 components, so that instead of there being only one solution in equilibrium with both of the salts with $R = 1·67$ and 2·33 at a given temperature, there would be a number of such solutions represented by a line on the isothermal diagram. This may be one reason for the difficulty in preparing pure $7Al_2O_3,3SO_3,xH_2O$.

When $5Al_2O_3,3SO_3,xH_2O$ has been air-dried the value of x is very close to 32. Crystals of the compound which have been washed only with water take an unexpectedly long time to reach constant weight when exposed to the air at room temperature. The weights at different times when plotted suggest that a rapid loss of weight due to free water is followed by a very much slower loss which ends when the composition corresponds to $5Al_2O_3,3SO_3,32H_2O$. The behaviour might be due to simple adsorption, to a zeolitic effect, or to the presence of a very unstable hydrate. The last possibility is ruled out because the original crystals still in their mother-liquor give the same *X*-ray diagram as the air-dry solid. Since the crystals are relatively large, it is more likely that the slow loss of water in the middle stage of the air-drying is due to zeolitic water rather than to surface adsorbed water, and the drying curves suggest that 3 or even more molecules of water may be involved in this way. Several equilibration experiments have indicated that two or three molecules of additional water can be taken up readily by the $5Al_2O_3,3SO_3,32H_2O$. It may be that the poor *X*-ray diagrams given by this compound are due to its zeolitic nature, since zeolitic water sometimes causes this sort of effect with compounds having layer-lattice structures.

The water in the wet crystals or the zeolitic water in the dry crystals gives rise to an amorphous " pattern " which is not visible against the lines of the crystalline framework but causes the photographs to have a dirty background just as those in question have. Even in $5Al_2O_3,3SO_3,32H_2O$ it is probable that some of the water is zeolitic, for a preparation of this salt obtained at 70° (see Table VII) contained rather less than $31H_2O$. The much clearer *X*-ray diagram which it gave corresponds to its much lower content of zeolitic water. On equilibration over the mother-liquors the air-dried solid regains some at least of the zeolitic water which has been lost. The air-dried crystals of this basic salt generally have a roughened, damaged appearance.

(3) $7Al_2O_3,3SO_3,xH_2O$.—This basic salt, with $R = 2{\cdot}33$, the most basic of all those obtained by us, was first obtained in very small amounts in the experiment quoted in Table III and discussed in Note 14 to that table. It is evidently closely related to $5Al_2O_3,3SO_3,xH_2O$ and probably has a similar type of structure. It is also formed from the glassy solid of two-liquid system I just as is $5Al_2O_3,3SO_3,xH_2O$. The *X*-ray diagrams of the two basic salts are also somewhat similar as regards both character and quality. This suggests that the air-dry $7Al_2O_3,3SO_3,33H_2O$ may result by loss of zeolitic water from a higher hydrate just as $5Al_2O_3,3SO_3,32H_2O$ appears to do.

$7Al_2O_3,3SO_3,xH_2O$ seems to be stable only in contact with solutions containing very low concentrations of Al_2O_3 and SO_3, which makes its preparation difficult. We have not yet succeeded in reproducing it in quantity at will. The composition found (Al_2O_3, 45·97; SO_3, 15·60%) is very close to that required by the formula $7Al_2O_3,3SO_3,33H_2O$ (Calc.: Al_2O_3, 46·13; SO_3, 15·51%).

The Basic Salts with R = 2·17 *and* 1·83 *and Double Salts of the Latter with Ammonium Sulphate* (Plate, Nos. 13—16).

These have only been obtained by the sol method and the procedure required is essentially the same in all cases. An aluminium chloride solution is treated gradually with ammonia with stirring so long as the precipitate first formed will redissolve owing to peptisation. It is best to use a fairly concentrated solution of aluminium chloride such as 10 g. of $AlCl_3,6H_2O$ in 20 c.c. of water, as the peptisation then occurs more readily and, for this quantity, one cannot in practice add more than about 31 c.c. of 3·2N-ammonia, which is four-fifths of that theoretically required to form $Al(OH)_3$. Use of rather less ammonia merely results in smaller yields of basic salt being obtained but does not affect its nature. It is not necessary to wait until peptisation is complete at room temperature. It is completed readily whilst the temperature is being raised to 100°. After addition of the ammonia the sol is boiled gently for 10 minutes. This converts the sol into a solution which no longer gives a curd of hydroxide on addition of ammonium sulphate. 5 Minutes' boiling is insufficient for this and gives a solution which produces about half as much curd with ammonium sulphate as is given by the unboiled sol, mixed with a correspondingly smaller amount of crystalline basic salt. Longer boiling than 10 minutes should generally be avoided as it lowers the yields of the compounds having $R = 2{\cdot}17$ or 1·83 owing to gradual formation of $5Al_2O_3,3SO_3,xH_2O$, a change which is usually complete after about an hour's boiling. After the 10 minutes' boiling the solution is filtered, if necessary, and stirred into a cold aqueous solution of ammonium sulphate. The nature of the crystalline compound which separates spontaneously on standing depends mainly upon the relative proportion of aluminium chloride and ammonium sulphate and only to a minor extent upon the actual concentrations. Special series of experiments showed that time of boiling and the basicity of the sols only altered the amount of the compound with $R = 2{\cdot}17$ or 1·83 which could be obtained but did not determine which of these actually separated. Neither could this be influenced by inoculation. It is clear that separation of these two basic salts, or the double salt with ammonium sulphate, does not depend upon the presence in the boiled solutions of two different ions or complexes one of which yields with sulphate ions the 2·17 compound while the other yields the 1·83 compound. All the evidence indicates that these two compounds are derived from one and the same ion or complex which is formed from the micelles of the sol by short boiling but is slowly converted by continued boiling into some other ion or complex which yields with sulphate ions $5Al_2O_3,3SO_3,xH_2O$.

With high concentrations of ammonium sulphate the 1·83 compound gives double salts, but apart from these it has not been possible to obtain any other very basic salts from the lightly boiled sols.

That a sol with different heat treatments can given two solutions giving two entirely different types of crystalline compound is of great interest. The solutions are not colloidal, but the very high basicity of the compounds which separate from them suggests that they must contain micelles approaching colloidal dimensions. They should repay further study.

Table VIII gives details of a number of preparations of the compounds with $R = 2{\cdot}17$ and 1·83 and the basic double salts I and II derived from the latter.

The Structures of the Basic Aluminium Sulphates.

Many basic salts are known to have layer-lattice structures which are related to those of the corresponding hydroxide and such, or related structures, seem far more probable for the very basic aluminium sulphates than those previously suggested (Bassett and Durrant, *loc. cit.*, p. 285). Aluminium hydroxide occurs in four different crystalline forms, and the rather

TABLE VIII.*

Preparations of compounds with R = 2·17 *and* 1·83 *and of basic double salts I and II* (Plate, Nos. 13—16).

(10 G. of $AlCl_3,6H_2O$ were used in each experiment.)

3·2N-NH_3, c.c.	Time sol was boiled, mins.	Vol. of sol boiled, c.c.	$(NH_4)_2SO_4$, g.	Total vol., c.c.	Wt. of solid obtained, g.	Actual *R* value found.	Composition of solid (air-dry), %. Al_2O_3.	SO_3.	NH_3.	Cl.
25·9	10	46	3	460	1·93	1·85	39·63	16·80	0·07	0·05
† 30	15	50	3	500	1·415	1·86	38·87	16·36	—	—
B30	10	130	5	1030	4·42	1·823	39·94	17·19	—	—
30	10	130	4	1030	4·36	1·87	39·63	16·66	—	—
30	10	130	3	1030	4·36	1·90	39·51	16·33	—	—
25	10	125	6	1025	2·80	‡ 1·844	39·13	17·42	0·33	—
30	10	130	6	1030	3·81	‡ 1·88	39·69	17·49	0·39	—
				Calc. for $11Al_2O_3,6SO_3,66H_2O$:			40·22	17·20		
				,, $11Al_2O_3,6SO_3,68H_2O$:			39·70	16·98		
25	0	100	1	900	Only curd obtained					
25	5	,,	1	,,	Half as much curd + salt with $R = 2·17$					
25	10	,,	1	,,	2·5	2·176	41·61	15·00		
25	20	,,	1	,,	2·02 } Not analysed but appearance showed that					
25	30	,,	1	,,	1·26 } both preps. consisted of salt with $R = 2·17$					
25	45	,,	1	,,	1·66	2·162	42·21	15·31	—	—
30	10	50	2	1000	1·76	2·17	42·68	15·42	—	—
Inoculated with 2·17-salt										
30	10	50	2	1000	1·75	2·15	42·34	15·45	—	—
Inoculated with 1·83-salt										
30	10	50	2	1000	1·87	2·15	41·04	14·95	—	—
Inoculated with $5Al_2O,3SO_3,xH_2O$										
30	10	50	2	1000	1·68	2·18	41·57	14·97	—	—
Inoculated with basic double salt I										
25 * ‖	10	125	1	1025	2·08	2·165	40·97	14·84	—	—
C30 * ‖	10	130	1	1030	3·22	2·176	41·40	14·92	—	—
30	10	50	1	2000	1·95	2·19	41·41	14·83	—	—
30	10	50	0·86	250	1·15	2·18	42·37	15·25	—	—
30	10	50	0·86	250	1·39	2·17	42·33	15·33	—	—
Inoculated with basaluminite										
				Calc. for $13Al_2O_3,6SO_3,76H_2O$:			41·77	15·12	—	—
				,, $13Al_2O_3,6SO_3,83H_2O$:			40·13	14·54	—	—
32	About 60 mins. at 70—80°.	132	3	530	3·58	1·68	40·22	18·76	0·84	—
D25·9	10	46	3	57	1·75	1·577	39·06	19·43 (air-dry)	1·33	0·38
							38·44	19·12 (equilibrated)	1·31	0·37
								on NH_4Cl-free basis		
							38·65	19·22	1·14	—
				Calc. for $(NH_4)_2SO_4\{11Al_2O_3,6SO_3,66H_2O\}$:			38·40	19·17	1·16	—
E30	10	50	50	100	3·703	—	30·41	25·87	5·64	0·26
					on NH_4Cl-free basis		30·44	25·90	5·52	—
				Calc. for $6(NH_4)_2SO_4\{11Al_2O_3,6SO_3,72H_2O\}$:			30·41	26·02	5·53	—

* For B, C, D, and E, see p. 2273.

† About half of the original solid seemed to be amorphous. 50 C.c. of 2N-HCl were stirred in which dissolved amorphous part almost at once; the liquid was decanted, and the residue washed. A lot of washing was required to remove all NH_3 (200 c.c.), which suggests that some of basic double salt I was present originally.

‡ These *R* values are obtained after deduction of SO_3 equivalent to the NH_3.

‖ See note (p. 2276) about the separation of $5Al_2O_3,3SO_3$ from these mixtures.

peculiar conditions needed to obtain the several basic sulphates suggest very strongly that these are derived from different forms of the hydroxide and that establishment of the appropriate hydroxide structure is a principal necessity in the preparation of the different basic salts, which could only exist in a very restricted sense, if at all, in solution. Now diaspore, α-Al_2O_3,H_2O, can be regarded as built up of infinite strips each formed by the parallel linkage of two chains of AlO_6 octahedra with one-third of the octahedral holes unoccupied by aluminium. In boehmite, γ-Al_2O_3,H_2O, the diaspore bands are linked together into sheets (see Wells, "Structural Inorganic Chemistry," 1945, pp. 356, 357, and Fig. 97). Hydrargillite, γ-$Al_2O_3,3H_2O$, is built up of layers of $Al(OH)_6$ octahedra with one-third of the octahedral holes unoccupied. The structure of bayerite, α-$Al_2O_3,3H_2O$, has not been determined but it seems likely that the same layers of $Al(OH)_6$ octahedra are present. Although we have never observed the actual formation of diaspore in our experiments, it is reasonable to suppose that the irregular micelles of aluminium hydroxide sols are converted into bands or strips of the type characteristic of diaspore during the 10 minutes' boiling of the sols which is required for the preparation of the basic salts with R values of 1·83 and 2·17 and that these compounds have lattice structures derived from diaspore. The same change could probably occur slowly at room temperature, which would account for the fact that these basic salts can also be obtained in small amounts from sols which have not been boiled at all (Bassett and Durrant, *loc. cit.*, p. 291). The lattices derived from the diaspore structure appear to be saturated with sulphate in the compound $11Al_2O_3,6SO_3,xH_2O$, although the compound $13Al_2O_3,6SO_3,xH_2O$ is also stable in presence of a considerably smaller proportion of sulphate. This more basic compound is, however, readily converted into $11Al_2O_3,6SO_3,xH_2O$ by increasing the proportion of sulphate, and this is why the double salts formed with ammonium sulphate are always derived from $11Al_2O_3,6SO_3,xH_2O$ and not from $13Al_2O_3,6SO_3,xH_2O$. The ease with which $11Al_2O_3,6SO_3,xH_2O$ gives these double salts is a good reason for thinking that simple basic salts having the diaspore bands in their lattice do not exist with R smaller than 1·83. Formation of the boehmite structure is slow at room temperature, but much more rapid at 100°. This change would occur during the hour's boiling of the sols which is normally required for good yields of $5Al_2O_3,3SO_3,xH_2O$ to be obtained. This suggests that this salt has a structure based on that of boehmite. Since unheated basic aluminium sulphate solutions formed by method (iii) can yield crystals of $5Al_2O_3,3SO_3,xH_2O$, it would appear that their nature is essentially similar to that of solutions obtained by boiling the sols. Action of excess of alkali leads to formation of hydrargillite or bayerite. The latter is usually obtained by the use of ammonia, and the former by means of sodium hydroxide. Sheets having the hydrargillite structure are present in kaolinite. The field evidence suggests that aluminite and basaluminite, which are frequently associated in their occurrences, have been formed by the action of sulphuric acid or aluminium sulphate solutions upon clay or marl. A reasonable inference is that these two minerals probably have layer-lattice structures derived from hydrargillite.

The basic sulphates with R equal to unity or less may contain either chains of AlO_6 octahedra or even simpler structures (see pp. 2246, 2252, 2254).

The maximum theoretical yield obtainable by the sol method from 10 g. of $AlCl_3,6H_2O$ would be 5 g. of the salt with $R = 1·83$ or rather less than 4 g. of the salt with $R = 2·17$. The variation in yields obtained in the various experiments summarised in Table VIII is due to some extent to such factors as time of standing and amount of stirring between addition of ammonium sulphate and filtration of the basic salt. The supersaturation of the mixtures only breaks down slowly and the rate of separation of the various basic salts depends a great deal upon the number of nuclei of the separating salt which are present and the extent to which they are stirred up. An endeavour was made to keep these factors as similar as possible in any one set of experiments and not to filter off the product until separation seemed to be complete. Apart from variations due to such causes the tabulated results indicate that (in addition to the conclusions already drawn on p. 2271) an increased proportion of ammonia improves the yield of any one compound when other factors remain constant. It also appears that the lower the basicity and the more concentrated the sols the shorter the boiling which is needed to cause the changes which produce $5Al_2O_3,3SO_3,xH_2O$.

The ratio of $AlCl_3,6H_2O$ to $(NH_4)_2SO_4$ as well as the final concentration of the latter both seem to have some influence on the nature and yield of the compound obtained. There is considerable latitude allowable in the conditions of preparation of all the compounds but those employed in the experiments marked A, B, C, D, E in Tables VI and VIII seem on the whole to be the most satisfactory.

The compound with $R = 2·17$ is the easiest to obtain in the pure state owing to its

insolubility and inability to give double salts with ammonium sulphate. The compound with $R = 1{\cdot}83$ is more difficult to get pure because the conditions under which the pure compound or basic double salt I can separate from solution do not differ greatly.

The chief difficulty in the case of $5Al_2O_3,3SO_3,xH_2O$ is to get it quite free from amorphous material, as has been mentioned on p. 2267.

The compound with $R = 1{\cdot}83$ was obtained in good yield as follows: 10 G. of $AlCl_3,6H_2O$ in 200 c.c. of water were precipitated cold with a small excess of ammonia. Hydroxide was filtered off at the pump on a hardened filter-paper and washed with 200 c.c. of water to remove most of the ammonium chloride. The fairly hard cake was then well mixed with a spatula into 5 g. of $AlCl_3,6H_2O$ in 50 c.c. of water. Most of it peptised fairly quickly and after standing overnight had given a clear sol. This was boiled for 10 minutes, cooled by standing in cold water, and filtered from a trace of insoluble matter. A solution of 6·52 g. of " AnalaR " $Al_2(SO_4)_3,16H_2O$ (*i.e.*, the amount equivalent to 5 g. of $AlCl_3,6H_2O$) in 20 c.c. of water was then stirred fairly quickly into the sol. At first the mixture remained clear, but as the addition of sulphate proceeded it began to get milky and then rapidly became semi-solid after 15 c.c. of the sulphate solution had been added. 25 C.c. of water were added before completing the addition of sulphate. The precipitated solid was found to consist entirely of very minute needle-like prisms, so small and thin that it was difficult to see any double refraction. After 4 hours' standing it filtered off quickly and well on a Buchner funnel and was washed with 32 c.c. of cold water, followed by 10 c.c. of absolute alcohol and air-dried. Yield 3·7 g. (Found: Al_2O_3, 39·05; SO_3, 16·27%; $R = 1{\cdot}88$). It also contained 0·06% of NH_3. The *X*-ray diagram was exactly like other preparations having *R* of about this value [compare the experiments (i) and (ii) quoted by Bassett and Durrant (*loc. cit.*, pp. 290, 291)]. In those experiments the sols had not been heated at all, and it would seem that the amorphous (curd) phase of two-liquid system II is related to the crystalline basic salts with $R = 2{\cdot}17$ and 1·83 in much the same way that the glassy phase of two-liquid system I is related to the salt with $R = 1{\cdot}67$.

The compound having $R = 1{\cdot}83$ forms at least two double salts with ammonium sulphate. These are $[(NH_4)_2SO_4][11Al_2O_3,6SO_3,xH_2O]$ (x = about 66) and $6(NH_4)_2SO_4[11Al_2O_3,6SO_3,xH_2O]$ (x = about 72) and will be referred to as " basic double salt I " or " II ." The first of these forms well-developed flat prisms with square ends extinguishing at an angle of 12° to the sides of the prism. This enables it to be distinguished readily from the compounds having $R = 1{\cdot}83$ or 2·17, as well as from $5Al_2O_3,3SO_3,xH_2O$ since all of these form prisms showing straight extinction.

Two prisms of double salt I are often twinned or intergrown at right angles to their length, giving a characteristic Maltese cross.

" Basic double salt II " forms very well-developed and often large, transparent octahedra and tetrahedra. The angles of these are about those of the cubic system but these crystals show strong double refraction and are probably orthorhombic.

" Basic double salt I " is obtained very readily in good crystals and in good yield by the sol method from similar solutions to those which yield the compounds mentioned above. If the double salt is desired it is better to use a more concentrated solution and a higher proportion of ammonium sulphate. If it is not wanted it is better to use a more dilute solution with less ammonium sulphate though, even then, there is always a possibility of some of the double salt separating. This appears to be the case more particularly with preparations of the salt having $R = 1{\cdot}83$—probably because this is one constituent of basic double salt I.

By long-continued washing of basic double salt I with cold water the whole of the ammonia can be removed as sulphate from this double salt, but there occurs at the same time further hydrolysis of the basic sulphate so that the final, ammonia-free residue has $R = 2{\cdot}17$ and gives a sharp *X*-ray diagram identical with that of crystals having this value of the ratio but prepared directly. In the early stages of the washing it is probable that the ammonia-free basic salt which results is in an amorphous state, for a considerable proportion of the ammonium sulphate can be removed with little or no effect on the *X*-ray diagram which remains that of the basic double salt. Considerable solution of basic salt occurs during this hydrolytic washing, and if the washings are allowed to stand for some days a small amount of well-formed prisms of the compound with $R = 2{\cdot}17$ separates.

This decomposition and hydrolysis on washing of basic double salt I, slow though it is, makes the determination of its precise formula a little difficult. Prepared as in the experiments quoted by Bassett and Durrant and washed with about 50 c.c. of cold water, its *R* value is usually very close to 1·67 or, after deduction of SO_3 equivalent to the NH_3, to 1·86. Further washing increases both these ratios. This disturbance was minimised as far as possible in the following preparation: 20 g. of $AlCl_3,6H_2O$ in 40 c.c. of water were treated slowly and with stirring with 51·8 c.c. of 3·2N-ammonia, heated for 10 minutes to approximately 100°, and filtered from a little insoluble matter. 6 G. of ammonium sulphate in 20 c.c. of water were added. After standing undisturbed for 21 hours, there was a considerable crystalline deposit which adhered to the sides and bottom of the beaker so that the solution could be decanted with practically no loss of solid. The latter was washed by decantation in the beaker with several very small amounts each of 20%, 50%, 75%, and absolute alcohol. Even the 20% alcohol threw down a slight white precipitate (though small amounts of water did not) but by decanting this away the washed solids was not contaminated. The solid was finally detached from the beaker with a nickel spatula and air-dried; yield, 3·51 g. Some of the air-dried solid was equilibrated over some of the mother-liquor but only increased in weight by 1·7%.

		Al_2O_3, %.	SO_3, %.	NH_3, %.	Cl, %.
Found	air-dry	39·06	19·43	1·33	0·38
	equilibrated	38·44	19·12	1·31	0·37

The composition of the double salt on the ammonium chloride-free basis is :

	$(NH_4)_2SO_4$, %.	Al_2O_3, %.	SO_3 (total), %.
	4·48	38·65	19·22
Calc. for $(NH_4)_2SO_4[11Al_2O_3,6SO_3,66H_2O]$:	4·52	38·40	19·17

The *R* value for the double salt is 1·58, or 1·835 after deduction of SO_3 equivalent to NH_3 not balanced by Cl. The presence of the ammonium chloride is to be attributed to the somewhat inefficient washing. The latter has avoided any decomposition of the double salt, and the experiment shows that the basic constituent really has a relatively simple formula, which at first seemed doubtful.

The mother-liquors from the above preparation of basic double salt I, after 41 hours' heating at about 80°, had given a large deposit consisting of fairly large crystals of a rough appearance and apparently showing straight extinction. These crystals filtered easily and were washed with a very little water, then with 50%, 75%, and absolute alcohol and air-dried; yield 5·49 g. They gave a good "alunite" *X*-ray diagram in spite of a very abnormal composition. This case is discussed under "alunite" (see p. 2255, Notes 1 and 2).

Basic double salt I can also be prepared by the action of ammonium sulphate on previously prepared $11Al_2O_3,6SO_3,xH_2O$. This is best done in presence of some of the mother-liquor from which the 1·83-compound has crystallised since, if plain water is used, there is some hydrolysis with formation of small amounts of amorphous matter which make it difficult to obtain a pure preparation of the basic double salt.

Basic Double Salt II : $6(NH_4)_2SO_4[11Al_2O_3,6SO_3,xH_2O]$.

There are three methods by which this double salt can be prepared : (i) by the sol method directly, boiling for only 10 minutes and using a high concentration of ammonium sulphate; (ii) by the action of a solution of ammonium sulphate on basic double salt I; (iii) by the action of a concentrated solution of ammonium sulphate on the compound $11Al_2O_3,6SO_3,xH_2O$.

Method (i) is by far the best and simplest, but the other two are of interest as showing the close relationship of the three compounds. It is difficult to get quite pure preparations owing (*a*) to the ease with which ammonium sulphate is leached from the crystals and (*b*) to the formation of small amounts of amorphous basic products of hydrolysis which contaminate the crystals. This is due to the fact that, since none of the basic aluminium sulphates can form congruent solutions, any one of them is further hydrolysed to some extent by water or salt solutions. It is a serious cause of trouble when using methods (ii) and (iii) above. It could be avoided by using a solution of ammonium sulphate not in plain water but in the mother-liquor from which either of the salts $11Al_2O_3,6SO_3,xH_2O$ or $(NH_4)_2SO_4[11Al_2O_3,6SO_3,xH_2O]$ has crystallised. Difficulty (*a*) can be entirely overcome by restricted washing with suitable wash-liquors but the final product is usually contaminated with a trace of ammonium chloride. Method (i) was carried out as follows : To 10 g. of $AlCl_3,6H_2O$ in 20 c.c. of water were added fairly quickly with stirring 30 c.c. of 3·11N-ammonia. The mixture was heated quickly and peptisation was complete before it started to boil. It was boiled gently for 10 minutes and then cooled by standing the beaker in a trough of cold water. After filtration from traces of insoluble matter and dilution to 100 c.c., 50 g. of ammonium sulphate were added and dissolved by warming; the clear solution was then left undisturbed at room temperature. Crystallisation began after an hour, and a large deposit of fair-sized brilliant tetrahedra gradually formed on the sides and bottom of the beaker. Crystallisation appeared to be complete after 88 hours, and the whole of the mother-liquor was then removed by decantation. The loosely adherent crystals were then scraped on to a disc of hardened filter-paper on a small conical filter-funnel. After thoroughly draining on the pump, they were washed in succession with 3 c.c. of water, 50% and 75% alcohol, all three-quarters saturated with ammonium sulphate, and finally with absolute alcohol. The yield of air-dried crystals was 3·7 g. They consisted entirely of clear, fairly large (1—2 mm.) and well-formed doubly refracting tetrahedra quite free from alum crystals. Analysis gave the following results (in %) :

	Al_2O_3.	SO_3 (total).	NH_3.	Cl.	$(NH_4)_2SO_4$.
Found	30·41	25·87	5·64	0·26	—
On NH_4Cl-free basis this become	30·44	25·90	5·52	—	21·42
Calc. for $6(NH_4)_2SO_4[11Al_2O_3,6SO_3,72H_2O]$	30·41	26·02	5·53	—	21·47

The decantate from the double salt had by the next day deposited a little more of the double salt, but this was mixed with much ammonium alum, and in preparing this double salt it is necessary to be on one's guard against contamination with alum.

Basic double salt II is the compound obtained by Bassett and Durrant (*loc. cit.*, p. 293) in very small yield in the form of bright doubly refracting octahedra. The formula suggested by them, *viz.*, $2(NH_4)_2SO_4,5Al_2O_3,3SO_3,34H_2O$, from analysis of only 0·037 g. of the crystals is certainly incorrect.

The double salt is sometimes obtained in doubly refracting tetrahedra and sometimes in doubly refracting octahedra. Any one preparation generally consists entirely of either the one or the other but not of a mixture of the two types of crystals. The *X*-ray diagrams of the tetrahedral and octahedral forms are identical.

A preparation of basic double salt II from basic double salt I was carried out as follows : 1 G. of basic double salt I, 5 g. of ammonium sulphate, and 5 c.c. of water were shaken at 25°. After 18 days the prisms of the original double salt had all been converted into small doubly refracting octahedra of basic double salt II but much solid ammonium sulphate was also present. A further 5 c.c. of water had to be added before the latter had all dissolved after further shaking at 25°. A small amount of amorphous flocculent material was also present, which accounts for the rather high Al_2O_3 content of the preparation. The octahedral crystals were separated by decantation to remove as much as possible of the amorphous material and were then filtered off on the pump, washed with 2 c.c. of 60% and then 1 c.c. of absolute

alcohol and air-dried. Weight 1·13 g. [Found : Al_2O_3, 31·03; SO_3, 26·04; NH_3, 5·59% (= 21·70% $(NH_4)_2SO_4$)].

In another somewhat similar experiment the basic double salt I was not converted into the basic double salt II when shaken at 25° with a solution of 3·75 g. of ammonium sulphate in 12·5 c.c. of water but was converted by one containing 6·25 g. in 12·5 c.c. of water. A sample of $5Al_2O_3,3SO_3,32H_2O$ with $R = 1·67$ remained unaltered and gave no crystals of basic double salt II when shaken for a month at 25° with a saturated solution of ammonium sulphate. This is additional evidence that the structure of $5Al_2O_3,3SO_3,xH_2O$ must differ fundamentally from that of the compounds having $R = 1·83$ and 2·17. On the other hand, the sol obtained from 10 g. of $AlCl_3,6H_2O$ in 85 c.c. of water and 29 c.c. of 3·2N-ammonia after being heated to 100° for 40 minutes gave a good yield, 3·4 g., of basic double salt II after addition of 50 g. of ammonium sulphate in 100 c.c. of water. This result indicates that 40 minutes' heating to 100° of the very basic sol has been insufficient to destroy the condition which leads to precipitation of the compounds with $R = 1·83$ or 2·17 or their double salts and to give rise to one which permits $5Al_2O_3,3SO_3,xH_2O$ to separate. The less basic the sol the shorter appears to be the time of heating needed for this change to occur.

The change occurs to a very small extent, however, even after only 10 minutes' heating of very basic sols. The two mixtures marked with asterisks in Table VIII from which good yields of the salt with $R = 2·17$ had been separated had deposited, after 6 weeks' standing, a considerable amount of amorphous material in which were numerous small transparent square crystals. These were twins. They were bright between crossed nicols when the sides of the square were parallel to the cross-wires, and extinguished in hour-glass fashion when the diagonals of the square were parallel to the cross-wires. The clear liquid was decanted from the solid sediment. The two lots of the latter were combined, and 14 c.c. of 2N-hydrochloric acid were stirred into the total volume of 120 c.c. The amorphous solid dissolved, and the crystals were filtered off on the pump, washed with 15 c.c. of water and then 8 c.c. of alcohol and air-dried. The crystals (0·11 g.) gave the *X*-ray diagram of $5Al_2O_3,3SO_3,xH_2O$. It is quite clear that in all these basic aluminium sulphate solutions complex equilibria exist between many ionic, molecular, and even micellar species. These equilibria can be shifted and modified by heating or other treatment, but their existence tends to make the preparation of individual pure compounds a matter of considerable difficulty.

The fact is important that, in the case of both basic double salt I and II, the basic aluminium sulphate part of the double salt corresponds exactly to $11Al_2O_3,6SO_3,xH_2O$ when due precautions are taken to avoid decomposition. This makes it practically certain that the variation in the value of R between the limits 1·83 and 1·90 for the ammonia-free basic salt is due to the presence of small amounts of basic products of hydrolysis. As these products are amorphous they have practically no effect on the *X*-ray photographs. They result either from decomposition of small amounts of basic double salt I originally present as an impurity in the salt with $R = 1·83$ or by decomposition of the latter salt itself. 0·5 G. of this salt which had $R = 1·88$ was washed exhaustively with 200 c.c. of water on an ordinary conical funnel and filter-paper. The residue on the paper then had $R = 1·99$ and could be seen under the microscope to consist of a mixture of amorphous material and well-formed prisms of the compound having $R = 2·17$. The latter had clearly crystallised from solution in the funnel during the washing, and some more had crystallised from the filtrate. A small quantity of this salt (0·0453 g.), crystallised from solution in this way, was equilibrated at 25° over the solution from which it had separated. It absorbed 3·2% of water during this process and then gave on analysis Al_2O_3, 40·04; SO_3, 14·75% (Calc. for $13Al_2O_3,6SO_3,83H_2O$: Al_2O_3, 40·13; SO_3, 14·54%).

The compound with $R = 2·17$ is very resistant to further hydrolysis. 0·5686 G. of this salt with $R = 2·14$ was washed slowly with 400 c.c. of water (at room temperature). The washings contained in all 0·0038 g. Al_2O_3 and 0·0041 g. SO_3; $R = 0·725$. The removal of these amounts of Al_2O_3 and SO_3 would have raised the R value of the residue to 2·22. The *X*-ray diagram of the washed material was almost identical with that of the original apart from a slight blurring of the central lines owing to formation of amorphous material.

There is no evidence that $5Al_2O_3,3SO_3,xH_2O$ or the compounds with $R = 1·83$ and 2·17 or any double salts derived from these have ever been found as minerals. Bassett and Durrant (*loc. cit.*, p. 292) thought that the 2·17-compound might correspond to a mineral which had been recorded under the name of felsöbányite. This view is not tenable, however, for we have been able to determine the *X*-ray diagram of a British Museum specimen (B.M. 40280) of this rare mineral from Felsöbánya, Szatmár, Hungary (= Baia Sprie, Crisana şi Maramures, Romania). It occurs in this specimen as an incrustation on stibnite and appears to consist of radial groups of prisms. The *X*-ray diagram indicates the presence of some amorphous material but according to Mr. Bannister it is essentially that of allophane, $Al_2SiO_5,5H_2O$.

This work was started at the end of 1935 at the suggestion of Dr. M. P. Applebey who has taken a continued interest in it; further, various members of his staff at Billingham, and in particular Messrs. A. M. Clark and H. N. Wilson, gave information and assistance. Although most of the *X*-ray work connected with the investigation was carried out by one of the authors (T. H. G.), a considerable amount was done by Dr. G. H. Cheesman at Reading, and also by Mr. D. Clark of the Research Dept., Billingham. Dr. F. A. Bannister and Dr. M. Hey of the British Museum gave invaluable help in connection with the mineralogical bearings of the research. It is a pleasure to thank all of these for their assistance and Imperial Chemical Industries Ltd. and Messrs. Peter Spence & Sons Ltd. for generous apparatus and money grants.

Practically the whole of the experimental work recorded in this paper was carried out in the Chemical Dept. of the University of Reading, but a few of the last experiments have been done at Widnes.

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Appendix.

The *X*-ray photographs to which the data in Table IX relate were taken with a 6-cm. camera, using Cu-*K*α radiation, some by Dr. T. H. Goodwin and some by Dr. G. H. Cheesman. The measurements of the lines were made by Miss M. Kolasa in Dr. Goodwin's laboratory at the University of Glasgow. Only the first 10—15 lines are recorded though from 40 to 56 lines were actually measured in different cases down to spacings of about 1 A. Intensities were measured visually the value 10 being given to the strongest line, and ½ to one only just visible. Proportional values were assigned to other lines. *b*, *bb*, or *bbb* signifies broad or diffuse, *u* uncertain.

Table X relates to the *X*-ray diagrams of the series of alunites of Table IIA. These photographs were taken by Mr. D. Clark of the I.C.I. Research Department, Billingham with a 19-cm. camera using Cu-*K*α radiation. He also measured the lines. Intensities were measured visually; *s* signifies strong, *m* moderate, *w* weak, (*b*) broad, (*d*) diffuse. In these tables the spacings are recorded down to about 1·5 A., but all which were fainter than very weak (*vw*) are omitted. Far more spacings were actually measured, and reflections down to 5° could be observed.

In all the tables the spacings, *d*, are given in Ångström units.

Table IX.

(1) $Al_2(SO_4)_3,16H_2O$, alunogen, from Chile (see p. 2246 for analysis). No. 1 on Plate.*

d.	*I.*	*d.*	*I.*
13·96	8	4·37	10 *b*
9·41	2 *bbb*	3·91	9
7·11	7	3·62	7
6·49	3	3·42	5 *u*
5·96	3	3·32	6 *u*
4·83	4	2·97	8 *bb*

(2) $Al_2O_3,2SO_3,11H_2O$. No. 2 on Plate.

d.	*I.*	*d.*	*I.*
6·99	9	4·23	4
5·80	7	4·00	10
5·36	4 *u*	3·87	5 *u*
4·98	8	3·73	10
4·53	8	3·52	3

(3) $5Al_2O_3,6SO_3,46H_2O$. Specimen with $R = 0·805$ (see Table II). No. 3 on Plate.

d.	*I.*	*d.*	*I.*
12·96	8	4·48	8
10·85	9	4·08	10
9·69	6 *u*	3·80	4 *u*
8·33	10	3·61	6
7·24	8	3·33	7
5·92	6	3·16	5 *u*
5·55	7	2·99	8
4·93	6		

* The *X*-ray diagrams of very pure synthetic $Al_2(SO_4)_4,16H_2O$ and of the mineral alunogen appear to be identical in all respects. There are indications of a faint and fuzzy line of spacing 9·41 A. but it is considered unlikely that this belongs to $Al_2(SO_4)_4,16H_2O$.

(4) $5Al_2O_3,6SO_3,40H_2O$. Specimen with $R = 0·824$ (see Table II). No. 4 on Plate.

d.	*I.*	*d.*	*I.*
14·21	10	4·22	7
10·85	4	3·90	5
8·23	7	3·57	6 *bb*
7·38	7	3·08	4
6·67	3	2·91	6
6·23	4	2·77	6
5·19	6 *b*	2·55	4
4·62	7		

(5) $Al_2O_3,SO_3,9H_2O$, aluminite, from Halle, Saxony (see p. 2252). No. 5 on Plate.

d.	*I.*	*d.*	*I.*
9·25	9	3·80	10
7·72	10	3·49	6
6·45	8	3·23	4
5·49	6	3·12	7
4·98	7	2·93	5
4·69	7	2·75	6
4·35	9	2·53	3

(6) $Al_2O_3,SO_3,6·78H_2O$. No. 6 on Plate.

d.	*I.*	*d.*	*I.*
11·88	7 *bbb*	3·62	8
7·67	9	3·22	8 *b*
6·63	7	3·03	7
6·01	6 *bbb*	2·75	7 *b*
4·64	9	2·59	5
4·27	10	2·45	5

(7) $Al_2O_3,SO_3,5H_2O$. No. 7 on Plate.

d.	*I.*	*d.*	*I.*
7·72	8	5·00	4
7·04	7	4·44	5
6·58	4	4·21	4
6·18	4	4·00	10
5·89	4	3·77	3
5·27	3	3·65	3

(8) $Al_2O_3,SO_3,4H_2O$. No. 8 on Plate.

d.	*I.*	*d.*	*I.*
9·60	10 *b*	2·77	5
7·05	6	2·65	4
5·96	5	2·56	½
4·78	10 *bb*	2·48	3
3·83	9 *b*	2·34	7
3·45	6	2·19	7
3·18	7	2·11	½
2·95	10 *bb*		

(9) Australian alunite (see section 17 for analysis). No. 9 on Plate.* †

d.	*I.*‡	*d.*	*I.*‡
10·24	4 *u*	2·45	3
7·32	4 *u*	2·30	2
5·62	5	2·26	7
4·92	7	2·20	4
3·46	6	2·01	2
3·28	1 *bu*	1·89	7
2·99	10 *b*	1·82	½
2·85	3		

* The lines with spacings 10·2 and 7·3 A. were undoubtedly present in the *X*-ray photos of both Australian alunite and one preparation of synthetic potassium alunite which were taken at Reading. As other workers have failed to detect these two lines, they are probably not due to alunite.

† No. 10 on Plate is the diagram of synthetic ammonium alunite, the first preparation given in Table IIA. The measurements of this diagram are given in section 18.

‡ See also Pabst (*Amer. Min.*, 1947, **32**, 29).

TABLE IX (*continued*).

(10) $7Al_2O_3,3SO_3,33H_2O$ (measured by T.H.G.). The photograph was not considered good enough for reproduction.

d.	*I.*	*d.*	*I.*
13·8	8	3·64	4
11·6	10	3·51	4
8·73	8	3·28	—†
6·71	6	2·77	4†
5·96	4	2·500	4
5·05	4*	2·400	2
4·60	—*	2·306	2
4·23	6	2·400	2
3·86	4		

(11) $2Al_2O_3,SO_3,xH_2O$, Basaluminite (see pp. 2251 and 2265).‡ No. 11 on Plate.

d.	*I.*	*d.*	*I.*
12·15	10	3·81	6 *bb*
9·05	9	3·58	7
7·01	5 *bbb*	3·41	6
5·82	6	3·19	5
5·25	6	3·03	5 *bbb*
4·64	9 *b*	2·78	4

(12) $5Al_2O_3,3SO_3,32H_2O$. Specimen with $R = 1{\cdot}60$ (see Table VII). No. 12 on Plate.

d.	*I.*	*d.*	*I.*
14·66	9	4·98	4
11·69	10	4·64	1 *u*
8·86	7	4·41	1 *u*
7·26	5	4·27	6
5·65	3	3·98	5
5·28	2	3·77	6

* Limits of a band of lines, 2 lines. † Limits of a band of lines.

‡ The *X*-ray diagram and these measurements relate to the material associated with aluminite (iii).

(13) $11Al_2O_3,6SO_3,xH_2O$. No. 13 on Plate.

d.	*I.*	*d.*	*I.*
11·25	10	3·89	6
9·39	6	3·52	4
7·10	5	3·35	3
5·68	½	3·17	5
5·27	2	2·94	½
4·68	8	2·86	6
4·29	3 *u*	2·73	4

(14) $13Al_2O_3,6SO_3,xH_2O$. No. 14 on Plate.

d.	*I.*	*d.*	*I.*
12·15	10	3·80	5
9·89	9	3·56	5
8·77	6	3·29	5 *b*
7·00	3	3·01	4
5·88	4	2·86	3
5·25	3 *b*	2·67	6
4·45	7 *b*	2·43	2 *b*
4·12	6		

(15) $(NH_4)_2SO_4[11Al_2O_3,6SO_3,xH_2O]$. No. 15 on Plate.

d.	*I.*	*d.*	*I.*
11·08	10	3·96	7
8·62	6	3·69	3
7·05	5	3·53	3
5·79	5	3·41	3
4·80	7 *b*	3·24	6
4·24	7	3·10	3

(16) $6(NH_4)_2SO_4[11Al_2O_3,6SO_3,xH_2O]$. No. 16 on Plate.

d.	*I.*	*d.*	*I.*
11·29	10	3·97	5
9·59	5	3·75	2
5·91	5	3·45	3
5·55	2 *u*	3·29	6
4·91	4	3·08	2
4·41	7	2·96	5

TABLE X.

Alunites of Table IIA.

Sections 18 and 24 relate to photographs taken with a 6-cm. camera and measured by Miss Kolasa

(17) Australian alunite* from Bulladelah, near Newcastle, N.S.W.†

d.	*I.*
5·723	*mw*
4·975	*ms*
3·491	*m* +
2·984	*s*
2·871	*w*
2·473	*vw*
2·280	*ms*
2·190	*w*
1·897	*ms*
1·741	*ms*
1·643	*vw*
1·564	*vw*
1·498	*m* +

(18) Ammonium alunite of Note 1. No. 10 on Plate.

d.	*I.*
5·73	4 *u*
4·93	9
4·18	3 *u*
3·80	2 *u*
3·61	1 *u*
3·46	5
3·25	2 *u*
2·97	10
2·85	1
2·48	1
2·28	4
2·19	2
1·92	1
1·90	6
1·73	5
1·64	2
1·56	2 *b*
1·49	4 *b*

(19) Ammonium alunite of Note 2.

d.	*I.*	*d.*	*I.*
8·819	*m*	2·305	*ms*
7·479	?	2·217	*mw*
6·819	*w*	2·133	*vw*
5·825	*mw*	2·104	*vw*
5·001	*vs*	2·060	*vw*
4·619	*w*	2·007	*w*
4·343	*m* +	1·946	*vw*
4·202	*m*	1·909	*vs*
3·859	*m*	1·874	*vw*
3·666	*m*	1·848	*w*
3·512	*s*	1·818	*w*
3·325 } 3·253 }	*mw*(*b*)	1·750	*s*
		1·674	*vw*
2·999	*vvs*	1·652	*m*
2·912	*w*	1·581	*mw*
2·862	*w*	1·568	*mw*
2·797	*w*	1·513	*ms*
2·661	*vw*	1·498	*m*(*d*)
2·491	*mw*		

* Analysis of Australian alunite (by J. Anderson): Al_2O_3, 38·2; Fe_2O_3, 0·03; K_2O, 10·0; Na_2O 1·55; CaO, 0·12; TiO_2, trace; SO_3, 37·8; P_2O_5, 0·38; SiO_2, 1·5; H_2O (direct determination), 11·0; total 100·58% [H_2S and $(NH_4)_2S$ groups absent; MgO absent].

† See note to section 9 of Appendix.

TABLE X (*continued*).

(20) Ammonium alunite of Note 3.

d.	*I.*
5·836	*mw*
5·001	*vs*
3·504	*m* +
3·005	*vvs*
2·921	*vw*
2·865	*vw*
2·493	*vw*
2·322	*m* +
2·215	*w*
1·952	*mw*
1·908	*s*
1·750	*ms*
1·651	*mw*
1·585	*w*
1·570	*w*
1·520	*m*
1·502	*mw*

(21) Ammonium alunite of Note 4.

d.	*I.*
5·859	*w*
5·017	*s*
3·512	*m* +
3·008	*vs*
2·929	*vw*
2·868	*vw*
2·495	*vw*
2·321	*m* +
2·221	*w*
1·949	*mw*
1·914	*ms*
1·752	*m* +
1·654	*mw*
1·586	*w*
1·572	*vw*
1·519	*m*
1·503	*w*

(22) Ammonium alunite of Note 5.

d.	*I.*
5·813	*mw*
5·009	*s*
3·508	*m* +
3·002	*vs*
2·800	?
2·497	*vw*
2·328	*m*
2·300	*m*
2·220	*w*
1·958	*vw*
1·911	*ms*
1·752	*m* +
1·652	*mw*
1·586	*vw*
1·571	*vw*
1·523	*m*
1·506	*m*(*b*)

(23) Ammonium alunite of Note 6.

d.	*I.*
5·859	*w*
5·017	*s*
3·512	*m* +
3·008	*vs*
2·929	*vw*
2·868	*vw*
2·495	*vw*
2·321	*m* +
2·221	*w*
1·949	*mw*
1·914	*ms*
1·752	*m* +
1·654	*mw*
1·586	*w*
1·572	*vw*
1·519	*m*
1·503	*w*

(24) Potassium alunite of Note 7.*

d.	*I.*
10·10	5 *bbu*
7·37	4 *bbb*
5·49	5
4·97	5
4·78	7
4·03	4 *bbb*
3·51	4
3·41	6
2·94	10
2·79	3
2·43	1
2·23	7
2·17	4
1·98	1
1·88	8
1·72	6
1·62	3
1·54	3
1·49	1

(25) Potassium alunite of Note 8.

d.	*I.*
5·734	*mw*
4·950	*s*
3·508	*ms*
2·984	*vvs*
2·846	*w*
2·469	*vw*
2·263	*ms*
2·210	*mw*
1·904	*s*
1·752	*ms*
1·647	*w*
1·562	*w*
1·508	*w*
1·489	*ms*

(26) Potassium alunite of Note 4.

d.	*I.*
5·756	*mw*
4·975	*s*
3·516	*ms*
2·987	*vvs*
2·841	*w*
2·473	*vw*
2·258	*ms*
2·217	*mw*
2·018	*vw*(*b*)
1·907	*ms*
1·753	*m* +
1·651	*vw*
1·561	*w*
1·509	*w*
1·491	*w*

(27) Sodium alunite of Note 4.

d.	*I.*
5·679	*w*
4·901	*vs*
3·496	*s*
3·428	*vw*
2·958	*vvs*
2·915	*m*
2·844	*w*(*b*)
2·775	*m*
2·445	*vw*
2·212	*vs*
1·896	*vs*
1·870	*w*
1·848	*m*
1·746	*s*
1·644	*m*
1·554	*mw*
1·538	*m*
1·505	*w*

* See note to section 9 of Appendix.

(28) Sodium alunite of Note 9.

d.	*I.*
5·690	*mw*
4·909	*vs*
3·845	*vw*?
3·496	*s*
3·005 }	*vvvs* (*b*)
2·935 }	
2·904	*w*
2·841	*vw*
2·775	*m*
2·439	*w*
2·209	*vs*
1·891	*vs*
1·867	*w*
1·846	*m*
1·745	*s*
1·712	*vw*
1·665	*vw*
1·643	*m*
1·602	*vw*
1·554	*mw*
1·537	*m*
1·504	*w*
1·497	*w*

(29) Sodium alunite of Note 10.

d.	*I.*
7·186	*vvw*?
5·690	*m*
4·901	*vs*
4·486	*m*
4·343	*m*
3·925	*w*
3·508	*ms*
2·973	*vvs*
2·852	*vw*
2·797	*m*
2·453	*w*
2·228	*s*
1·900	*s*
1·861	*m*
1·747	*s*
1·647	*m*
1·559	*mw*
1·544	*m*
1·505	*mw*
1·482	*m*

481. *Preparation of Organo-cobalt Compounds.*

By D. L. Ingles and J. B. Polya.

Organo-cobalt bromides and iodides have been prepared by the interaction of Grignard compounds of the 1-naphthyl and 2-naphthyl series with cobalt halides in ethereal solution. The compounds are tetraco-ordinated. Some physical and chemical properties of the compounds are described.

Attempts have been made to prepare organo-cobalt compounds by thermal decomposition of cobalt toluene-*p*-sulphinate, thermal decomposition of phenyldiazonium cobaltinitrite (Hodgson and Marsden, *J.*, 1944, 22) in acetone, thermal and catalysed decomposition of the black cobalt chloride adducts of diazonium chlorides, the boiling of diphenyliodonium iodide with finely divided cobalt powder in propanol (Makarova and Nesmeyanov, *Izv. Akad. Nauk S.S.S.R.*, Chem. Class, 1945, 617), the boiling of aromatic compounds with cobalt acetate and aliphatic alcohols in a Dean–Stark apparatus, the boiling of phenyl bromide with pyrophoric cobalt powder in anisole or pyridine, direct cobaltation of furfuraldehyde with cobalt acetate in the presence of mercuric acetate, and heating di-1-naphthylmercury with cobalt halides. All these attempts failed, although in some cases traces of benzene-soluble organic materials with varying cobalt contents were obtained (Ingles, Ph.D. Thesis, University of Tasmania).

When anhydrous cobalt bromide or cobalt iodide in ethereal solution was added to RMgX (R = 1-naphthyl or 2-naphthyl; X = Br or I) dark green precipitates were obtained. The extraction of such precipitates with cold benzene gave green or blue-green solutions which deteriorated on storage and deposited black, blue, or green solids of varying composition. Addition of light petroleum or dioxan in excess to the benzene solutions afforded organic cobalt compounds of the types $RCoX_3$, R_2CoX_2, $RCoX_3,R_2CoX_2$, and, in one instance, R_3CoI. Magnesium (up to 11%) was found in the products obtained by using this technique. When the Grignard compounds were added to the cobalt halide solutions, the organo-cobalt compounds were obtained free from magnesium. The compounds could be purified by reprecipitation from ethereal solution. The compounds were shown to be organometallic by decomposition with water or dilute acids which afforded mainly dinaphthyls (Gilman and Lichtenwalter, *J. Amer. Chem. Soc.*, 1939, **61**, 957; Kharasch and Fields, *ibid.*, 1941, **63**, 2316; Kharasch and Tawney, *ibid.*, p. 2308; Kharasch and Lambert, *ibid.*, p. 2315) in addition to cobalt hydroxide and cobalt salts. Most of the isolated dinaphthyls were impure, which indicates that hydrolytic and thermal decomposition may occur simultaneously; further work will be necessary to clarify this matter.

RMgBr and cobalt iodide or RMgI and cobalt bromide gave the organo-cobalt iodides. Similar observations have been made on the reaction of platinum chloride with methylmagnesium iodide (Pope and Peachey, *J.*, 1909, **95**, 571) and of phenylmagnesium bromide with chromium chloride (Hein, *Naturwiss.*, 1940, **28**, 93). The residue left after extraction of the crude reaction products of the Grignard compounds and cobalt halides with cold benzene did not contain metallic cobalt. The benzene extracts are not identical with the organo-cobalt compounds which have been finally isolated, since the latter are practically insoluble in benzene. Light petroleum precipitates compounds of the types $RCoI_3$ and $R_3Co_2Br_5$. The latter may be written tentatively as $RCoBr_3,R_2CoBr_2$. Dioxan precipitates R_2CoX_2; these compounds are obtained in poorer yields than the foregoing since they are not quite insoluble in dioxan, which slowly decomposes all organo-cobalt compounds hitherto investigated. Through decomposition in dioxan the organo-cobalt compounds tend towards an empirical formula of the type R_3CoX, but no compound of this type could be isolated in sufficient purity.

The organo-cobalt compounds are unstable; the iodides are more unstable than the bromides, and the R_2CoX_2 compounds more than the others. The compounds decompose on heating without definite melting points. Approximate temperatures of decomposition have been noted. Sublimation in a vacuum leads to decomposition with the liberation of free halogen. All the compounds are insoluble in benzene or light petroleum, slightly soluble in chloroform, soluble in ether, and slightly soluble in dioxan with decomposition. Molecular weights could not be determined by the usual methods but special techniques are being evolved for this purpose and it is proposed to report on this later. In view of the tetramerism of alkylplatinum halides (Rundle and Sturtevant, *J. Amer. Chem. Soc.*, 1947, **68**, 1561) it is possible that polymerism will be demonstrated also for the organo-cobalt compounds. Magneto-chemical measurements could not be carried out owing to lack of suitable equipment (offers of

assistance have been recieved from other Institutes but the difficulties of storing and mailing the unstable compounds have not yet been overcome). All the bromides are blue, the $RCoI_3$ compounds yellow-green, and the R_2CoI_2 compounds reddish-brown.

Silver nitrate quantitatively removes halogen. Attempts to prepare halogen-free organo-cobalt compounds, possibly involving cobalt chains, by reaction of our products with sodium or powdered potassium (Gilman and Lichtenwalter, *J. Amer. Chem. Soc.*, 1938, **60**, 3085) were unsuccessful.

Grignard compounds prepared from methyl iodide, ethyl iodide, propyl iodide, *iso*propyl iodide, and phenyl bromide were brought into reaction with cobalt halides and worked up as indicated before. The products had approximately the correct cobalt : halogen ratios required by the types noted in the naphthyl series. The absolute values were low, but the discrepancy could be explained by assuming molecular association between the organo-cobalt compounds and integral (1 or 2) numbers of benzene molecules. Substitution of 1-chloronaphthalene for benzene in an experiment with ethylmagnesium iodide and cobalt iodide has afforded a compound of the empirical formula $EtCoI_3,C_{10}H_7Cl$. The organo-cobalt compounds of the naphthyl series do not contain benzene, since reprecipitation from ether does not significantly alter the analytical figures. The organo-cobalt compounds of the phenyl and aliphatic series were impure. They require further study.

The yields varied considerably from experiment to experiment. Maximum yields will be quoted in the experimental section. The yields appear to decrease in the order : 1-naphthyl, 2-naphthyl, phenyl, aliphatic series; iodides, bromides; $RCoI_3$, $R_3Co_2Br_5$, R_2CoX_2.

Analogous experiments with iron and nickel halides were unsuccessful. The final products contained magnesium but no iron or nickel.

Experimental.

Naphthyl-cobalt Compounds.

Naphthyl halides (20 g.) were converted into the Grignard compounds with the calculated amounts of magnesium in ether (100 c.c.). The clarified Grignard solution was added to a solution of anhydrous cobalt halide (1—5% excess) in ether (300 c.c.) at room temperature, and the mixture heated under reflux for 15 minutes. The dark green precipitate was freed from ether by decantation and suction in vacuum. Benzene (100 c.c.) was added, with exclusion of air. After storage overnight, the coloured benzene solution was filtered and made up to a known volume, and 10-c.c. portions were used for further experiments. Yields are calculated on this basis. In some experiments which afforded unstable compounds in very small and variable yields no yields are quoted. In all such cases the yields are estimated as <1% unless indicated otherwise.

1-*Naphthylmagnesium iodide and cobalt iodide.* Addition of light petroleum (b. p. 40—60°, 50 c.c.) precipitated yellow-green crystals, decomp. 150—160° (Found : Co, 10·1; I, 68·0. $C_{10}H_7I_3Co$ requires Co, 10·3; I, 67·5%); yield 2·68 g., 60%. Decomposition with water gave 1 : 1′-dinaphthyl, m. p. 158° (m. p. of picrate 143°), and cobaltous hydroxide and iodide in the ratio 1 : 5. Addition of dioxan (50 c.c.) to the benzene extract gave a reddish-brown *dinaphthylcobalt di-iodide*, decomp. 150° (Found : Co, 10·8; I, 44·5. $C_{20}H_{14}I_2Co$ requires Co, 10·3; I, 44·8%). This was decomposed by water to give a mixture of hydrocarbons (m. p. of picrate 112°), and cobaltous hydroxide and iodide in the ratio 63 : 37. 1-*Naphthylcobalt tri-iodide* slowly dissolved in dioxan with a red colour. The iodine content of the residue gradually decreased to 24·2% (*tri*-1-*naphthylcobalt iodide*, $C_{20}H_{21}ICo$, requires Co, 22·4%.)

1-*Naphthylmagnesium iodide and cobalt bromide.* The same products were obtained as above but the yield of $RCoI_3$ was only 2%.

1-*Naphthylmagnesium bromide and cobalt iodide.* The same products were obtained but the yield of $RCoI_3$ was 25%, and R_2CoI_2 was isolated in a yield of 1·23 g. (55%).

1-*Naphthylmagnesium bromide and cobalt bromide.* Light petroleum precipitated blue crystals, decomp. 120° (Found : Co, 13·3; Br, 45·0. *Tri*-1-*naphthyldicobalt pentabromide* requires Co, 13·2; Br, 45·0%). Water decomposed this to impure hydrocarbons (m. p. of picrate 115°) and cobaltous hydroxide and bromide; yield 0·06 g., 2%. Dioxan precipitated a blue *compound*, decomp. 120° (Found : Co, 12·8; Br, 33·7. $C_{20}H_{14}Br_2Co$ requires Co, 12·4; Br, 33·8%).

2-*Naphthylmagnesium iodide and cobalt iodide.* Light petroleum precipitated yellowish-green crystals of *naphthylcobalt tri-iodide*, decomp. 160° (Found : Co, 10·8; I, 67·2. $C_{10}H_7I_3Co$ requires Co, 10·3; I, 67·5%). Decomposition by water gave impure aromatic material, m. p. 145° (m. p. of picrate 155°). Dioxan precipitated reddish-brown *di*-2-*naphthylcobalt di-iodide*, decomp. 90° (Found : Co, 10·8; I, 44·5. $C_{20}H_{14}I_2Co$ requires Co, 10·3; I, 44·8%). M. p. of picrate of decomposition products in aqueous filtrate, 150°.

2-*Naphthylmagnesium iodide and cobalt bromide.* The same results were obtained as in the preceding experiment.

2-*Naphthylmagnesium bromide and cobalt iodide.* The same results were obtained as in the preceding experiments but the yield of $RCoI_3$ was 47%.

2-*Naphthylmagnesium bromide and cobalt bromide.* Light petroleum precipitated blue crystals, decomp. 150—160° (Found : Co, 13·0; Br, 46·0. $C_{20}H_{21}Br_5Co_2$ requires Co, 13·2; Br, 45·0%); yield, 0·28 g., 9%. M. p. of the picrate of the decomposition products in water, 142°. Dioxan precipitated blue crystals of the *dibromide*, decomp. 65° (Found : Co, 12·8; Br, 33·7. $C_{20}H_{14}Br_2Co$ requires Co, 12·4; Br, 33·8%). M. p. of picrate of decomposition products in water, 153°.

Other Cobalt Compounds.

Experiments using the same technique and on the same scale were applied to phenyl bromide and aliphatic iodides.

Phenylmagnesium bromide and cobalt bromide. Light petroleum gave a blue solid (Found: Co, 14·4; Br, 51·8. $PhCoBr_3,C_6H_6$ requires Co, 13·0; Br, 52·8%). Dioxan gave another blue solid (Found: Co, 12·0; Br, 36·5. Ph_2CoBr_2,C_6H_6 requires Co, 13·1; Br, 35·5%). The yields did not exceed 4%. The *compounds* were impure and were not further investigated.

Methylmagnesium iodide and cobalt iodide. Dioxan precipitated a brown oil which was decomposed by water to cobalt hydroxide with evolution of gas. Light petroleum precipitated yellowish-green crystals (Found: Co, 9·9; I, 60·5. $MeCoI_3,2C_6H_6$ requires Co, 9·7; I, 62·3%). Water decomposed them to cobalt hydroxide with evolution of gas.

Ethylmagnesium iodide and cobalt iodide. Dioxan precipitated a brown oil. Light petroleum precipitated a yellow-green solid (Found: Co, 10·5; I, 61·7. $EtCoI_3,2C_6H_6$ requires Co, 9·5; I, 60·9%).

1-Chloronaphthalene being used instead of benzene, light petroleum precipitated yellowish-green crystals (Found: Co, 10·2; I, 60·2. $C_3H_5I_3Co,C_{10}H_7Cl$ requires Co, 9·3; I, 60·3%). The *compound* contained 1-chloronaphthalene, which separated on decomposition in water (m. p. of picrate, 136°). Cobalt hydroxide and gas were also formed.

n-*Propylmagnesium iodide and cobalt iodide.* Dioxan gave a brown oil. Light petroleum precipitated a yellowish-green solid (Found: Co, 9·4; I, 66·3. $C_3H_7I_3Co,C_6H_6$ requires Co, 10·2; I, 67·9%).

iso*Propylmagnesium iodide and cobalt iodide.* Dioxan gave an oil. Light petroleum precipitated a yellowish-green solid (Found: Co, 9·2; I, 67·3. $C_3H_7I_3Co,C_6H_6$ requires Co, 10·2; I, 67·9%).

The yields of the aliphatic organo-cobalt compounds varied between 4 and 8%. Decomposition in water occurred qualitatively in the same manner with all of them. Owing to combination with solvent, the decomposition points were not significant. Decomposition occurred around 130° in each case, but solvent must have been lost at lower temperatures.

Analysis.—The sample was decomposed with concentrated hydrochloric acid, and the dissolved cobalt determined by precipitation with 1-nitroso-2-naphthol. Alternatively, the sample was ignited and weighed as Co_3O_4. Halogen was determined by the Volhard method. N-Silver nitrate solution rapidly removes the halogen of organo-cobalt compounds on gentle heating. After experiments with mixed halides, the silver halide precipitate was tested to check the homogeneous nature of the halogen; mixed silver halides were never observed.

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UNIVERSITY OF TASMANIA, HOBART. [*Received, March 31st*, 1949.]

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482. *The Formation of Isomeric Azo-compounds in the Coupling of Diazonium Salts with* 1-*Naphthylamine.*

By HAROLD S. TURNER.

The mixtures of 2- and 4-arylazo-1-naphthylamines formed by coupling benzene- and substituted benzene-diazonium salts with 1-naphthylamine have in several cases been separated by adsorption chromatography, and the components isolated and characterised. The absorption spectra of these compounds over the range 220—580 mμ. have been determined.

GATTERMANN and LIEBERMANN (*Annalen*, 1912, **393**, 198) coupled various substituted benzenediazonium compounds with 1-naphthylamine-5-sulphonic acid (Laurent's acid) and determined the ratio of the 2- and 4-isomers produced by reducing the mixture and separating the 1 : 2- and 1 : 4-naphthylenediamine-5-sulphonic acids by fractional crystallisation. They concluded that, in the coupling of benzenediazonium compounds with this acid, (*a*) the more negative the substitution of the diazo-component the greater the tendency to coupling in the 4-position (sulphanilic acid, coupling exclusively in the 2-position, was an exception), and (*b*) an increase in the acidity of the coupling medium favours coupling in the 2-position. The 2-isomers were not isolated from the mixtures which were usually produced.

It has long been realised that, similarly, when diazonium compounds are coupled with 1-naphthylamine a mixture of the 2- and 4-aminoazo-compounds is produced, in which the latter is the major component. The formation of the 2-aminoazo-compound is a source of loss when the aminoazo-compound is required as an intermediate in the preparation of polyazo-compounds, since the 2-aminoazo-compounds do not diazotise normally, and it has been claimed that suitable modification of the amino-group of 1-naphthylamine will suppress *o*-coupling. For example, formation of the methyl-ω-sulphonate or of the toluene-*p*-sulphonyl derivative is said to have this effect, and it is claimed that 1-sulphaminonaphthalene couples exclusively in the 4-position (Bayer, B.P. 238,683). Nevertheless, the simple 2-arylazo-1-naphthylamines have not been described in the literature, only those with additional substituents in the naphthalene nucleus having been obtained.

The mixtures of isomers obtained by coupling diazotised aniline and several substituted anilines (*p*-methyl-, *p*-methoxy-, *m*- and *p*-chloro-) with 1-naphthylamine have now been separated by adsorption chromatography on alumina. With the exception of diazotised *m*-chloroaniline, which was coupled in dilute hydrochloric acid, the couplings were carried out in aqueous acetic acid–sodium acetate. The chromatograms obtained were generally complex, often containing more than 12 distinct zones, the *o*- and *p*-aminoazo-compounds being the principal components. Most of the products of decomposition and of side reactions which gave rise to the minor zones were more strongly adsorbed than the two main products, and of these the *p*-compound was the more strongly adsorbed. The large number of products formed in addition to the *o*- and *p*-aminoazo-compounds can be ascribed to all the possibilities of diazo-interchange, of decomposition of the diazonium to hydroxyl compounds, and of subsequent coupling. In no case did the material recovered from these zones exceed 2·5% of the total weight of crude coupling product. There was no indication that diazoamino-compounds were present in the crude coupling products, even where coupling was carried out in aqueous acetic acid–sodium acetate, though trace quantities cannot be excluded. In general, the formation

FIG. 1.

Thermal diagram of 2- and 4-p-chlorobenzeneazo-1-naphthylamine.

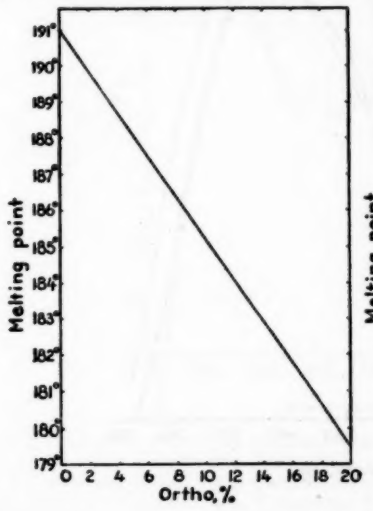
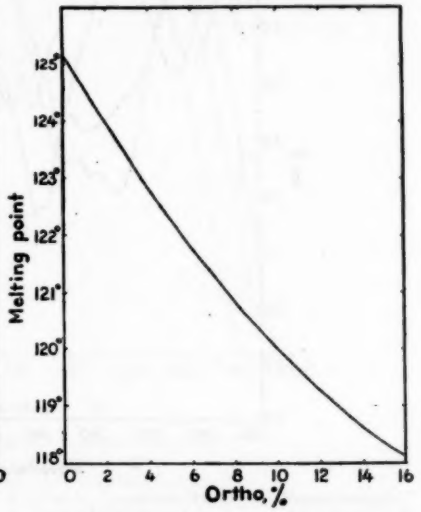


FIG. 2.

Thermal diagram of 2- and 4-p-methoxybenzeneazo-1-naphthylamine.



of 1-phenyl-3-naphthyltriazens occurs under these conditions only when the reactivity of the naphthyl radical is reduced by suitable substitution or direct blocking (cf. Dwyer, *J. Roy. Soc. N.S.W.*, 1940, **74**, 99; Morgan, *J.*, 1905, **87**, 86, 935). 1-Phenyl-3-naphthyltriazen has, however, been prepared by the interaction of α-azidonaphthalene and phenylmagnesium bromide (Dimroth, *Ber.*, 1906, **39**, 3905).

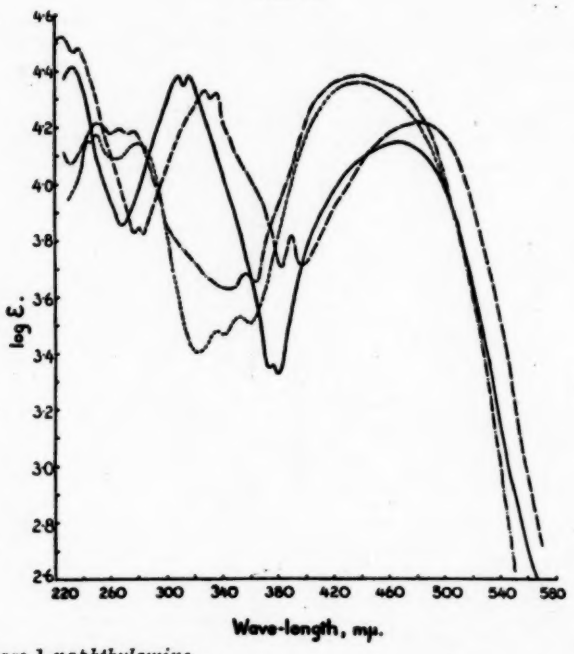
In the case of aniline, *p*-toluidine, and *m*-chloroaniline the recovery of combined *o*- and *p*-compounds from the coupling product was 95—100%, and here the proportion of the isomers was obtained by direct weighing. In the case of *p*-chloroaniline and *p*-anisidine the *p*-isomers appeared to decompose rapidly on the alumina, and the total recovery was 80 and 41%, respectively, though pure samples of each isomer were obtained. No extensive attempt was made to find a more suitable adsorbent. The proportions of the isomers were determined by constructing thermal diagrams (Figs. 1 and 2) from the pure isomers and referring to these the melting points of the crude coupling mixtures. This procedure suffers from the disadvantage that the coupling mixture contains compounds other than the *o*- and *p*-isomers, and so a falsely high value for the *o*-content would be expected. A rapid chromatographic separation was, therefore, attempted with the object of separating the combined adjacent *o*- and *p*-zones from the other products. The product, however, had a lower melting point than the crude mixture. There was, nevertheless, such a close correspondence between the apparent *o*-content of the crude coupling mixture as obtained from the melting point (which would in any case be in the nature of an upper limit) and as estimated from the actual quantity of *o*-isomer isolated from the

coupling mixture by the chromatographic separation (which would set a lower limit) that the method seems justified. Further, it may be deduced that the *o*-isomers were not appreciably decomposed during the separation.

The results obtained are summarised in Table I. From this it may be seen that, over the small range of compounds investigated, when a *p*-substituted benzenediazonium salt coupled with 1-naphthylamine in acetic acid–sodium acetate, the proportion of *o*-coupling increased with the electron-releasing character of the substituent. This parallels Gattermann and Liebermann's generalisation based on the coupling of Laurent's acid.

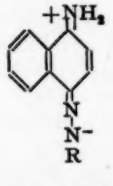
The simple 2-*benzeneazo*-1-*naphthylamines* have not previously been described. The orientation of the 2- and the 4-isomers was determined by conversion into the phenanthrazine, and into *NN'*-diacetyl-1 : 4-naphthylenediamine, respectively.

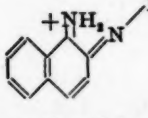
FIG. 3.



———— 2-*Benzeneazo*-1-*naphthylamine*.
— — — — 2-p-*Methoxybenzeneazo*-1-*naphthylamine*.
- - - - - - 4-*Benzeneazo*-1-*naphthylamine* (*cf., for example, Krüss*, Z. physikal. Chem., 1905, **51**, 257; *Shatenshtein*, Acta Physicochim. U.R.S.S., 1938, **10**, 121; 1940, **12**, 73).
—·—·— 4-p-*Methoxybenzeneazo*-1-*naphthylamine*.

In the analysis of the crude coupling mixtures obtained from diazotised *p*-toluidine and *p*-chloroaniline, three major zones were obtained instead of the usual two. The two more strongly adsorbed zones in each case gave the ordinary 4-isomer on elution and isolation. Here it would appear that partial (at least) separation into labile *cis*- and *trans*-isomers of the 4-isomer took place on the column (cf. Hartley, *J.*, 1938, 633; Cook, *J.*, 1938, 876; 1939, 1309; Zechmeister, Frehden, and Jörgensen, *Naturwiss.*, 1938, **26**, 495).

(I.) 

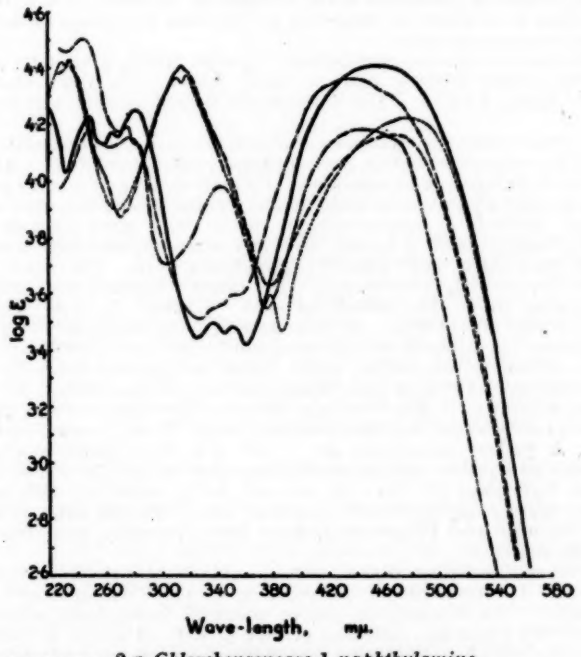


(II.)

The absorption spectra of these compounds in methanol have been determined over the range 220—580 mμ. The principal maxima are listed in Table II, and the spectra reproduced in Figs. 3 and 4. No attempt is made to analyse these spectra in detail, in the absence of the

spectra of suitable reference substances, but it is pointed out that, relatively to the *p*-isomers, there is in the *o*-isomers a general shift of the absorption maxima to longer wave-lengths. The *o*-isomers have a much greater total absorption in the ultra-violet region than the *p*-, and this probably indicates the presence of greater strain in their molecules. This would be expected from the ionic resonance structures possible in the two cases (I and II) (cf. Bergmann and Weizmann, *Trans. Faraday Soc.*, 1936, **32**, 1318), electromeric displacements in the former case involving the longer path. In the case of 2- and 4-nitro-1-naphthylamines, there are similar tendencies, the *o*-isomer having a much greater ultra-violet absorption (Hodgson and Hathway, *ibid.*, 1945, **41**, 115).

FIG. 4.



---------- 2-p-*Chlorobenzeneazo*-1-*naphthylamine*.
— — — — — 2-p-*Tolueneazo*-1-*naphthylamine*.
———————— 4-p-*Chlorobenzeneazo*-1-*naphthylamine*.
—.—.—.— 4-p-*Tolueneazo*-1-*naphthylamine* (*cf.* e.g., *Krüss*, loc. cit.).
—...—...— 1-p-*Tolueneazo*-2-*naphthylamine* (*cf.* e.g., *Krüss*, loc. cit.).

TABLE I.

Azo-1-*naphthylamines*, $R\cdot N{:}N\cdot C_{10}H_6\cdot NH_2$.

R =	Recovery, *o*- + *p*-, %.	Yield based on total, *o*- + *p*-. *o*-, %.	*p*-, %.	M. p., *o*-.	M. p., *p*-.	M. p., acetyl deriv. of *p*-.	Note.
Phenyl	94·75	7	93	161—161·5°	125°	242—243°	(1)
p-Tolyl	99·5	7	93	126	149—150	240—241	(1)
p-Methoxyphenyl	41	9·9	90·1	150·5—151·5	125·2	226—227	(1) (3)
p-Chlorophenyl...	80	5·8	94·2	171·5—172	191·0	254—255	(1) (3)
m-Chlorophenyl	96·5	8·1	91·9	151	121	240—241	(2)

(1) Acetate–acetic acid coupling medium.
(2) Dilute hydrochloric acid medium.
(3) Percentages of isomers from thermal diagrams.

EXPERIMENTAL.

(Microanalyses are by Mr. E. S. Morton. All m. p.s are uncorrected.)

Carefully purified intermediates were used in preparing the aminoazo-compounds. The alumina used was Spence's Grade " O ".

Coupling Procedure.—Diazotised *m*-chloroaniline was coupled by method B, all other diazotised amines by method A.

Method A. 1-Naphthylamine hydrochloride (0·025 g.-mol.) in water (80 c.c.) was added slowly to a sodium acetate–acetic acid solution (3·3N-sodium acetate, 0·33N-acetic acid; 25 c.c.) containing as a dispersing agent a polyglycerol oleic ester (50%; 1·0 c.c.) at 0° (external ice-cooling).

The amine hydrochloride (0·0251 g.-mol.), hydrochloric acid (*d* 1·18; 1·5 × 0·0251 g.-mol.), ice (10 g.), and water (30 c.c.) were treated with 2N-sodium nitrite to a starch–iodide end-point. The very slight excess of nitrous acid was removed by a little aqueous sulphamic acid. The diazonium solution thus obtained was added dropwise during ½ hour to the stirred ice-cold suspension of 1-naphthylamine, and stirring continued overnight at 0—2°. 2N-Sodium hydroxide was added to the suspension until it was alkaline to Clayton-yellow. The azo-compound was filtered off, washed very thoroughly, and the moist cake transferred with water (100 c.c.) to a Kilner jar. 2N-Sodium hydroxide (5 c.c.) was added, and the whole milled with porcelain beads for 24 hours. After being warmed to effect coagulation, the mixture was filtered, and the azo-compound thoroughly washed and vacuum-dried. The use of the dispersing agent to disperse the 1-naphthylamine minimises contamination by products of side reactions, but the final milling process with alkali is necessary to remove it as otherwise it appears to form a benzene-insoluble material with the aminoazo-compounds.

Method B. The diazonium solution was added dropwise during ½ hour to an ice-cold solution of 1-naphthylamine hydrochloride (0·025 g.-mol.) in water (150 c.c.), N-hydrochloric acid (2·0 c.c.), and polyglycerol oleic ester (50%; 1·0 c.c.). The mixture was stirred overnight at 0—2° and then worked up as before.

Separation of the Crude Coupling Mixtures.—(a) *Aniline → 1-naphthylamine.* The crude product (7·50 g.; m. p. 116—119°) in benzene (400 c.c.) was separated on a column (6·5 × 41 cm.). Development with benzene (22 l.) gave a chromatogram consisting of 2 main zones and several more strongly adsorbed minor zones. The zones were separated by draining and extrusion, and the adsorbed material extracted by pure methanol and isolated by evaporation *in vacuo*. The more strongly adsorbed zone gave 4-benzeneazo-1-naphthylamine (6·60 g.), and the less strongly adsorbed zone gave 2-*benzeneazo*-1-*naphthylamine* (0·50 g.). Both were chromatographically pure. The recovery was *ca.* 95%, of this *ca.* 93% being the *p*-, and 7% the *o*-isomer. The latter separated from benzene–light petroleum in deep orange-red plates, m. p. 161—161·5° (Found: C, 78·0; H, 5·35; N, 16·6. $C_{16}H_{13}N_3$ requires C, 77·75; H, 5·26; N, 17·0%). 2-Benzeneazo-1-naphthylamine was converted into the phenanthrazine as follows. A solution of the compound (0·05 g.) in 50% acetic acid (5·0 c.c.) and 10N-hydrochloric acid (0·25 c.c.) was boiled under reflux and treated carefully with zinc dust until colourless. The hot solution was filtered into sodium acetate solution (3·3N; 1·0 c.c.), and the residue rinsed with boiling water (0·5 c.c.). The combined filtrates were mixed with a solution of phenanthraquinone (0·05 g.) in sodium hydrogen sulphite solution (40%; 1·5 c.c.) and water (3·0 c.c.) and heated on the water-bath. A yellow precipitate of 1 : 2-3 : 4-5 : 6-tribenzphenazine was deposited, and crystallised from benzene as a yellow microcrystalline powder, m. p. 277—277·5° (Found: C, 87·3; H, 4·0; N, 8·3. Calc. for $C_{34}H_{14}N_2$: C, 87·4; H, 4·3; N, 8·5%), identical with an authentic specimen prepared from 1-*p*-tolueneazo-2-naphthylamine (Lawson, *Ber.*, 1885, **18**, 2421, gives m. p. 273°). Both samples dissolved in sulphuric acid to give an intense blue coloration, and their solutions in benzene showed a strong blue fluorescence.

The *p*-isomer was crystallised from carbon tetrachloride–light petroleum, and several times from benzene–light petroleum. It formed deep-red needles, m. p. 125° (Michaelis and Erdmann, *Ber.*, 1895, **28**, 2197, give m. p. 123°). The *N*-acetyl derivative separated from glacial acetic acid in deep-orange needles, m. p. 242—243° (Michaelis and Erdmann give m. p. 233°) (Found: C, 74·85; H, 5·5. Calc. for $C_{18}H_{15}ON_3$: C, 74·7; H, 5·22%). When this was reduced by sodium hydrosulphite (dithionite) and acetylated, *NN'*-diacetyl-1 : 4-naphthylenediamine was formed, identical with an authentic sample.

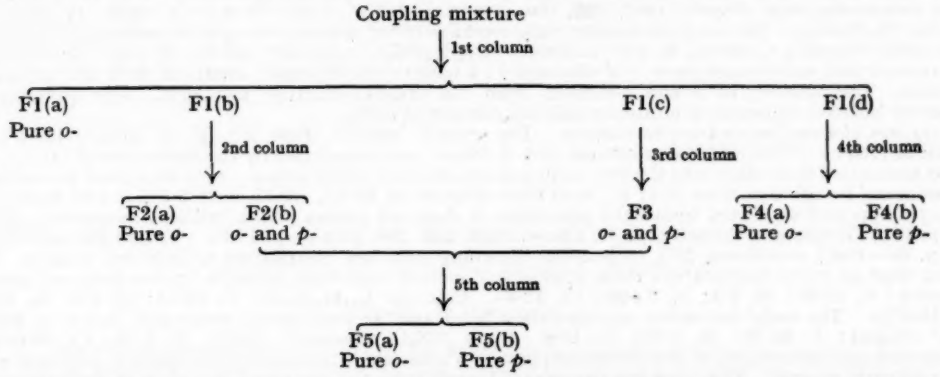
(b) p-*Toluidine → 1-naphthylamine.* The mixture of isomers (6·74 g.; m. p. 142—143°) was separated on a column (7 × 38 cm.). The chromatogram was developed (*a*) by carbon tetrachloride containing 3% by volume of ethyl acetate (7·5 l.), (*b*) by carbon tetrachloride containing 3% by volume of chloroform (7·5 l.), and (*c*) by carbon tetrachloride (2·5 l.) Separation into several minor and three well-defined major zones had occurred, the most strongly adsorbed of the latter being orange-yellow, the next maroon, and the next orange. The first of these on elution with methanol, followed by evaporation gave a product which was further separated on a small column, giving 3 small and a major red zone. The last yielded 4-*p*-tolueneazo-1-naphthylamine (0·50 g.). The second zone of the original chromatogram was chromatographically pure, and also gave the *p*-isomer (5·745 g.). The third zone gave a product which on further chromatographic separation gave a number of minor products and a major fraction, 2-p-*tolueneazo*-1-*naphthylamine* (0·465 g.), which crystallised from light petroleum (b. p. 80—100°) in red needles, m. p. 126° (Found: C, 78·1; H, 5·9; N, 16·35. $C_{17}H_{15}N_3$ requires C, 78·2; H, 5·75; N, 16·1%). It was converted into the phenanthrazine (m. p. 276—277°) as described above.

The *p*-isomer was crystallised from benzene–light petroleum, giving very deep-red needles, m. p. 149—150° (Weselsky and Benedikt, *Ber.*, 1879, **12**, 229, give m. p. 145°) (Found: C, 78·0; H, 5·65; N, 16·2%). The N-*acetyl* derivative crystallised from glacial acetic acid in orange-yellow needles, m. p. 240—241° (Found: C, 75·5; H, 5·7. $C_{19}H_{17}ON_3$ requires C, 75·2; H, 5·3%). This was converted into *NN'*-diacetyl-1 : 4-naphthylenediamine, identical with an authentic sample.

The recovery of *o*- and *p*-isomers was 6·71 g. or 99·5%, of which 93% was *p*- and 7% *o*-.

(c) p-*Anisidine → 1-naphthylamine.* The mixture of isomers (7·50 g.; m. p. 120·0°, shrinking above 105°) in benzene (250 c.c.) was separated on a column (65 × 7 cm.). Development with benzene (145 l.) gave a chromatogram showing 7 zones, the two principal zones, corresponding to the *o*- and the *p*-isomer, being most weakly adsorbed. The separation of the zones was not nearly complete, and a fractionation procedure was adopted as shown below. The chromatogram was divided into 4 fractions: F1(a) of pure *o*-isomer; F1(b), and *op*- mixture, largely *o*-; F1(c), an *op*-mixture, largely *p*-; F1(d), an *op*-mixture, containing only traces of *o*-, together with traces of zones corresponding to products of side reactions. These were treated as indicated in the scheme. F1(c) could not be separated on the third column, owing to the narrowness of the poorly defined zones; when it was combined with F2(b), a sharp and easy separation was achieved. Fractions F1(a), F2(a), F4(a), and F5(a) were chromatographically

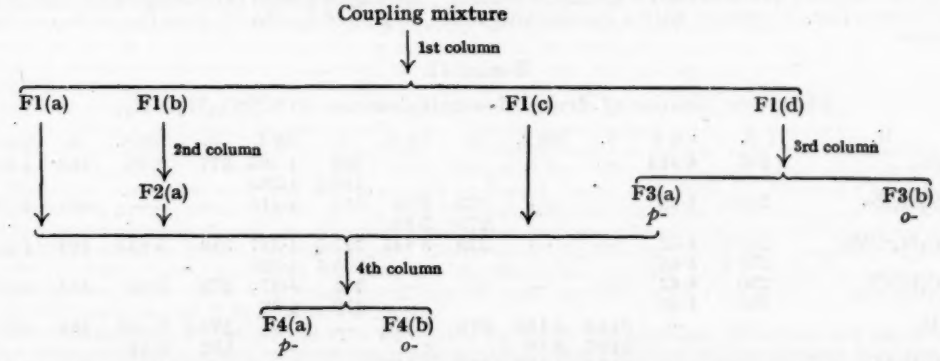
pure *o*-isomer (total : 0·73 g.). 2-p-*Methoxybenzeneazo*-1-*naphthylamine* crystallised from benzene–light petroleum in orange plates, m. p. 150·5—151·5° (not raised by further crystallisation from a variety of solvents) (Found : C, 73·4; H, 5·0; N, 15·3. $C_{17}H_{15}ON_3$ requires C, 73·65; H, 5·45; N, 15·15%). A sample was converted into the phenanthrazine, m. p. 277—278°, identical with an authentic specimen.



Fractions F4(b) and F5(b) consisted of *p*-isomer, but owing to decomposition during separation they were isolated in a tarry condition. A rapid re-separation on alumina, using benzene as developing solvent, gave a very complex chromatogram of 19 zones. Of these, 15 narrow zones, mainly purple or brown, were more strongly adsorbed than the principal zone of the *p*-isomer. This zone only was isolated, giving the *p*-isomer (2·33 g.) in a chromatographically pure condition. Crystallisation from light petroleum gave red needles, m. p. 125·2°. 4-p-*Methoxybenzeneazo*-1-*naphthylamine*, although mentioned in the literature, has not hitherto been analysed (cf. Vorländer, *Z. angew. Chem.*, 1930, **43**, 13; Weygand *et al.*, *J. pr. Chem.*, 1941, **158**, 266) (Found : C, 73·7; H, 5·35; N, 15·2%). The N-*acetyl* derivative, orange needles from glacial acetic acid, had m. p. 226—227° (Found : C, 71·35; H, 5·35; N, 13·4. $C_{18}H_{17}O_2N_3$ requires C, 71·5; H, 5·36; N, 13·16%). Reduction and acetylation gave *NN'*-diacetyl-1 : 4-naphthylenediamine, identical with an authentic sample.

The recovery of the isomers was only 41%. The recovery of *o*-isomer was equivalent to an *o*-content in the crude coupling of at least 9·7%.

(d) p-*Chloroaniline* → 1-*naphthylamine*. The mixed isomers (5·00 g.; m. p. 187·6°) in benzene (1 l.) were analysed on a column (7·5 × 40 cm.), benzene (23 l.) being used as developer. The incompletely resolved bands of *o*- and *p*-isomers were separated from impurities forming separate bands, and the adsorbed material recovered normally. It was re-separated on a similar column, and developed with benzene (30 l.). The three adjacent principal bands, red, maroon, and orange (in order of decreasing affinity for the adsorbent), were poorly defined. After extrusion, they were separated into 4 fractions (see following scheme), and the adsorbed materials recovered. F1(a) comprised most of the red zone with a little of a more strongly adsorbed zone of impurity. F1(b) included the remainder of the red zone and part of the maroon; F1(c) contained the rest of the maroon, together with a little of the orange; and F1(d) contained a little of the maroon plus all that remained of the orange zone.



A further separation of F1(b) was attempted on a smaller column. No separation took place under the same conditions as gave a separation of the crude mixture, and it appeared to be chromatographically pure. It was eluted from the column and recovered, giving F2(a). The red and the maroon zone are probably labile geometrical isomers of 4-*p*-chlorobenzeneazo-1-naphthylamine, incompletely separated on the column and isomerised by the isolation procedure here adopted. F1(d) was completely separated into 2 zones, F3(a) and F3(b), being *p*- and *o*-isomer, respectively. Finally, F1(a), F2(a), F1(c) and F3(a) were combined and re-separated on a column (7·5 × 40 cm.) and developed with benzene (75 l.). The two main zones were clearly defined and easily separated from one another and from 2 additional narrow zones of impurities.

In this way 2-p-*chlorobenzeneazo*-1-*naphthylamine* (0·28 g.) and its 4-isomer (3·71 g.) were isolated. The former crystallised from light petroleum in red needles, m. p. 171·5—172° (Found : C, 68·25; H, 4·2; N, 14·8; Cl, 12·75. $C_{16}H_{12}N_3Cl$ requires C, 68·25; H, 4·26; N, 14·9; Cl, 12·6%). It was converted into the phenanthrazine, m. p. 278—279°, identical with an authentic specimen.

The *p*-isomer separated from benzene–light petroleum in bright orange needles, m. p. 191·0° (Tröger and Petrowski, *Arch. Pharm.*, 1887, **225**, 160, give m. p. 187·5—188°) (Found : C, 68·0; H, 4·25; N, 14·55; Cl, 12·5%). The *acetyl* derivative, yellow-orange felted needles from glacial acetic acid, had m. p. 254—255° (Found : C, 66·85; H, 4·3; Cl, 10·85. $C_{18}H_{14}ON_3Cl$ requires C, 66·75; H, 4·35; Cl, 10·95%). Reduction and acetylation gave *NN'*-diacetyl-1 : 4-naphthylenediamine, identical with an authentic sample. The recovery of *o*- and *p*-isomers from the original mixture was 80%. The quantity of *o*-isomer isolated represents a minimum original content of 5·6%.

(e) m-*Chloroaniline* → 1-*naphthylamine*. The mixed isomers (6·00 g.; m. p. 109·5—112·5°) in benzene (250 c.c.) were added to a column (6·5 × 30 cm.) and developed by the same solvent (11 l.). A good separation took place into the two main and a number of minor zones. 4- (5·30 g.) and 2-*m*-chlorobenzeneazo-1-naphthylamine (0·47 g.) were thus obtained in 96·5% yield, with 8·1% *o*- and 91·9% *p*-. The *p*-compound separated from light petroleum in deep red prisms with a brilliant deep-green reflex, m. p. 121° (Tröger and Schaefer, *J. pr. Chem.*, 1926, **113**, 268, give m. p. 116°). From light petroleum (b. p. 80—100°) containing 20% of benzene the compound first crystallised in light-red needles. On being kept at room temperature these gradually dissolved and were replaced by the deep-red prisms (Found : C, 67·95; H, 3·9; N, 14·95; Cl, 12·45. Calc. for $C_{16}H_{12}N_3Cl$: C, 68·25; H, 4·3; N, 14·9; Cl, 12·6%). The *acetyl* derivative, orange-yellow felted needles from glacial acetic acid, had m. p. 240—241° (Found : C, 66·85; H, 4·05; Cl, 10·8. $C_{18}H_{14}ON_3Cl$ requires C, 66·75; H, 4·35; Cl, 10·95%). Reduction and acetylation of this compound gave *NN'*-diacetyl-1 : 4-naphthylenediamine, identical with an authentic sample. The 2-m-*chlorobenzeneazo*-1-*naphthylamine* separated from carbon tetrachloride–light petroleum in deep red needles, m. p. 151° (Found : C, 68·05; H, 4·35%). The phenanthrazine had m. p. 279°, and was identical with an authentic sample.

Thermal Diagrams.—Synthetic mixtures of the pure *o*- and *p*-isomers were prepared so as to cover the desired range and fused in carefully cleaned ignition tubes by immersion in an oil-bath approximately 10° above the m. p. of the pure *p*-isomer. The mixtures of *p*-chlorobenzeneazo-1-naphthylamines solidified to crystalline masses immediately on cooling; those of *p*-methoxybenzeneazo-1-naphthylamines formed glasses which became crystalline when scratched and kept at 40—50° for 12 hours. Owing to the intense colour of these mixtures it was not possible to detect the final disappearance of the solid phase in a conventional apparatus. The m. p.s were, therefore, taken on a heated-stage polarising microscope, the finely powdered specimens being spread thinly and uniformly between two carefully cleaned and dried microscope cover-glasses. The microscope was focussed on the edge of the aperture through the stage, and the specimen viewed between crossed polarisers. The stage could be heated at a rate of about 0·2° per minute in the desired region, and the m. p. was taken when a definite wave of extinction spread across the field of view from the edge of the aperture. Results were repeatable to within 0·1—0·2°. The diagrams obtained are reproduced in Figs. 1 and 2.

The mixture of isomers obtained by coupling *p*-anisidine with 1-naphthylamine was, without further purification, fused and ground in exactly the same manner as the synthetic mixtures; it melted at 120·0°. This corresponds to an *o*-content of 9·9%, in close agreement with the minimum value of 9·7% set by actual isolation. An attempt to separate the combined *o*- and *p*-isomers from impurities by means of a rapid chromatographic separation on alumina gave a product of m. p. 117·0—117·3° (corresponding to about 20% of *o*-), much lower, instead of higher, than the crude coupling mixture. The product so obtained was chromatographically less pure that the starting material.

The coupling mixture from *p*-chloroaniline was similarly treated. It melted at 187·6°, corresponding to 5·8% of *o*-, agreeing well with the 5·6% actually isolated. Here again a rapid chromatographic separation gave a more impure product, with a considerably lower m. p. (186·3—186·5°) than the crude coupling mixture.

TABLE II.

Absorption Maxima of Arylazo-1-naphthylamines, $R{\cdot}N{:}N{\cdot}C_{10}H_6{\cdot}NH_2$.

R.	λ.	log ε.	λ.	log ε.	λ.	log ε.	λ.	log ε.	λ.	log ε.	λ.	log ε.
2-C_6H_5	232	4·413	—	—	—	—	309	4·385	377	3·36	468	4·16
							315·5	4·385				
2-*p*-C_6H_4Me	235·5	4·43	—	—	273	3·88	315	4·415	—	—	468	4·17
					275 *	3·895						
2-*p*-$C_6H_4{\cdot}OMe$	223·5	4·52	—	—	279	3·845	327·5	4·327	389	3·815	469	4·219
	235·5	4·48					335·5	4·320				
2-*p*-C_6H_4Cl	230	4·42	—	—	—	—	312	4·37	379	3·60	480	4·23
	235	4·43					319	4·38				
4-C_6H_5	—	—	244·5	4·155	279	4·146	—	—	336·5	3·485	438	4·36
			249·5	4·18					352	3·53		
4-*p*-C_6H_4Me	—	—	247 *	4·175	278	4·155	—	—	340 *	3·55	440	4·37
			249	4·19					353 *	3·60		
4-*p*-$C_6H_4{\cdot}OMe$	—	—	250	4·215	265	4·195	—	—	357	3·685	435	4·385
					275	4·185						
4-*p*-C_6H_4Cl	—	—	249·5	4·23	265	4·175	—	—	338	3·495	458	4·408
					283	4·255			351·5	3·48		
1-*p*-Tolueneazo-2-naphthylamine	—	—	246	4·505	276	4·195	—	—	346	3·88	446	4·18
					283 *	4·14			373 *	3·58		

* = Point of inflexion.

Absorption Spectra.—The compounds, crystallised as described, were amply pure for these determinations. The solvent in every case was absolute methanol (AnalaR quality). The spectra of 2- and 4-*p*-tolueneazo-1-naphthylamine and of 1-*p*-tolueneazo-2-naphthylamine (added for comparison) were determined on a Beckman Photoelectric Spectrometer (Model DV) over the range 220—400 mμ. All other determinations in this region were carried out on an Adam Hilger " Spekker " Quartz Spectrophotometer. The author is indebted to Mr. I. Seltzer, who determined the absorption curves in the visible region (400—700 mμ.) on a Hardy Recording Spectrophotometer, using the same solutions as were used in the ultra-violet determinations. The maxima are listed in Table II, and the curves are reproduced over the range 220—580 mμ. (Figs. 3 and 4).

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483. *The Standard Electrode Potential of the Silver–Silver Chloride Electrode in Water–Glucose Mixtures.*

By M. H. EVERDELL.

The standard electrode potential of the silver–silver chloride electrode in various water–glucose mixtures has been determined, cells without liquid junction being used. The mean activity coefficients of hydrochloric acid in such solutions have been measured, and values for the distance of closest approach of ions in such solutions suggested.

THE silver–silver chloride electrode is being used as the reference electrode in an investigation into the change of certain electrode potentials in mixed solvents. Values of the standard electrode potential of this electrode in aqueous mixtures of alcohol, glycerol, or dioxan, etc., have been measured by various experimenters, but values of the potential in aqueous glucose mixtures are not on record.

EXPERIMENTAL.

Standard solutions of hydrochloric acid were made from redistilled hydrochloric acid and conductivity water. They were analysed by titration with borax, and the chloride content determined gravimetrically by precipitation with silver chloride.

To the hydrochloric acid solutions was added glucose of " AnalaR " grade, the mixture being made by weight. Immediately dissolution had been attained the solutions were placed in the cell and immersed in a thermostat controlled at 25°. Measurements were then made of the E.M.F. of cells of general type H_2|HCl, water, glucose, AgCl|Ag, a Cambridge potentiometer and a standard Weston cell made by the Cambridge Instrument Company being used.

Preliminary experiments had shown that precipitated silver chloride *in acid solution* is not reduced by glucose even after several days in the absence of light. It would appear therefore that silver–silver chloride electrodes should function satisfactorily in an aqueous hydrochloric acid–glucose solution. Notwithstanding this, and the fact that if such cells were set up steady values of E.M.F. were obtained some few minutes after introduction of the electrodes, if such cells were left for 8—30 hours large fluctuations in the measurements were found and these were not precisely reproducible. It is considered, however, that the non-reproducibility of results in aged cells is not due to deterioration of the silver–silver chloride electrodes but to bacterial action in the glucose solution, because (*a*) such errors remain if a " fresh " silver–silver chloride electrode is immersed in an aged solution, and (*b*) if the cell contains only a trace of hydrochloric acid in the presence of sufficient potassium chloride to maintain the conductance of the solution, the variation of E.M.F. as the solution ages during 1—2 days indicates an increase in hydrogen-ion concentration suggesting bacterial oxidation of the aqueous glucose to an acid product.

The values of E.M.F. were, however, found to be reproducible as long as they were measured 1—2 hours after dissolution of the glucose, and in no cases were the reported readings taken after that time.

Hydrogen electrodes were prepared according to Popoff, Kunz, and Snow (*J. Physical Chem.*, 1928, **32**, 1056), and hydrogen was purified by passage through soda–lime tubes and was saturated with water vapour, before entering the cell, by passage through water–glucose–hydrochloric acid solutions of the same composition as those in the electrolytic cell. Silver–silver chloride electrodes were prepared following Brown (*J. Amer. Chem. Soc.*, 1934, **56**, 646), and the electrodes obtained were all tested in pairs in the same aqueous hydrochloric acid solutions in cells of type Ag|AgCl (I) HCl AgCl|Ag (II) and all pairs which did not give zero E.M.F. were discarded.

All measurements of the glucose cells were made by use of two hydrogen electrodes and two silver–silver chloride electrodes, and each cell was made up twice. The recorded results represent therefore the mean values of at least four readings. The solutions were stirred except when the actual readings were taken. The densities of the various solutions were measured by means of a specific gravity bottle.

Results and Discussion.—Readings were obtained for various concentrations of hydrochloric acid in water–glucose mixtures containing 15, 25, 32, 40, or 50 g. of glucose per 100 g. of mixture. The barometric pressure was read at the time that each E.M.F. reading was made, and after allowance had been made for the water vapour pressure of such solutions at 25°, the observed E.M.F. readings were corrected to a partial pressure of hydrogen of exactly 1 atm. These

corrected values are recorded as the " observed " readings. In the following tables m represent the molality of hydrogen chloride, and ρ the density of the water–glucose mixtures; E and $E + (2RT/F) \ln m$ are recorded in volts.

15% Glucose solutions, $\rho = 1{\cdot}0608$.

E	0·3218	0·3468	0·3619	0·3831	0·3959	0·4103	0·4235	0·4501	0·4782	0·5181
m	0·1439	0·0858	0·0625	0·0400	0·0306	0·0225	0·01717	0·01000	0·00562	0·00250
$E + (2RT/F) \ln m$	0·2222	0·2206	0·2195	0·2177	0·2168	0·2158	0·2147	0·2135	0·2118	0·2103

25% Glucose solutions, $\rho = 1{\cdot}1042$.

E	0·3061	0·3382	0·3626	0·3819	0·3994	0·4156	0·4264	0·4599	0·4944
m	0·1646	0·0820	0·0491	0·03274	0·02285	0·01634	0·01305	0·00654	0·00326
$E + (2RT/F) \ln m$	0·2134	0·2097	0·2078	0·2062	0·2052	0·2042	0·2035	0·2015	0·2002

32% Glucose solutions, $\rho = 1{\cdot}1339$.

E	0·3271	0·3439	0·3540	0·3652	0·3780	0·3924	0·4161	0·3414	0·4606	0·5004
m	0·0900	0·0625	0·0506	0·0400	0·0306	0·02250	0·01374	0·01000	0·00562	0·00250
$E + (2RT/F) \ln m$	0·2034	0·2015	0·2007	0·1998	0·1988	0·1975	0·1958	0·1948	0·1930	0·1917

40% Glucose solutions, $\rho = 1{\cdot}1721$.

E	0·2997	0·3176	0·3362	0·3564	0·3760	0·3926	0·4088	0·4198	0·4536
m	0·1317	0·0900	0·06075	0·03929	0·02592	0·01828	0·01314	0·01044	0·00523
$E + (2RT/F) \ln m$	0·1955	0·1939	0·1923	0·1901	0·1883	0·1870	0·1862	0·1854	0·1837

50% Glucose solutions, $\rho = 1{\cdot}2254$.

E	0·2931	0·3049	0·3261	0·3505	0·3699	0·3868	0·4029	0·4139	0·4476
m	0·10975	0·02527	0·05465	0·03274	0·02175	0·01524	0·01095	0·00870	0·00435
$E + (2RT/F) \ln m$	0·1796	0·1784	0·1768	0·1748	0·1732	0·1718	0·1710	0·1702	0·1682

The E.M.F. of the cells measured may be expressed by the equation

$$E = E_0 - (2RT/F) \ln a_{\pm} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $a_{\pm}$ represents the mean activity of the electrolyte and E_0 the standard E.M.F. of the cell. Since by convention the standard electrode potential of hydrogen is taken as zero, E_0 represents the standard electrode potential of the silver–silver chloride electrode in the solvent considered.

There are various methods by which E_0 can be obtained from equation (1). The simplest follows Lewis and Randall (*J. Amer. Chem. Soc.*, **1921**, **43**, 1112), who rearranged the equation to the form

$$E + (2RT/F) \ln m = E_0 - (2RT/F) \ln \gamma_{\pm} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where $\gamma_{\pm}$ represents the mean activity coefficients of the electrolyte at molality m. A plot of the left-hand side of equation (2) against $m^{\frac{1}{2}}$ gives a line showing little curvature which on extrapolation to zero concentration gives E_0, since at zero concentration the mean activity coefficient equals unity. Owing to the facts that the values of the E.M.F. at very low concentrations are difficult to determine exactly, and that the graph shows a slight curvature, the extrapolation is not absolutely certain.

A more precise extrapolation, originally suggested by Brown and MacInnes (*ibid.*, 1935, **57**, 1356), is obtained for dilute solutions of uni-univalent electrolytes by means of the Debye–Hückel equation expressing the mean activity coefficient as follows:

$$-\log \gamma_{\pm} = \frac{Am^{\frac{1}{2}}}{1 + \beta a_i m^{\frac{1}{2}}} + \log \left(1 + \frac{2mM}{1000}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

In this equation $A = 1{\cdot}8123 \times 10^6 \rho^{\frac{1}{2}}/(DT)^{3/2}$ and $\beta = 50{\cdot}288 \times 10^8 \rho^{\frac{1}{2}}/(DT)^{\frac{1}{2}}$, where a_i is the distance of closest approach (in cm.) of the ions, ρ is the density of the solvent, D is the dielectric constant of the medium, and M is the mean molecular weight of the solvent $= 100/(X/M_x + YM_y)$, X and Y being the percentages of water and glucose, respectively, and M_x and M_y their molecular weights.

Substituting equation (3) in equation (2) and representing

$$\frac{4{\cdot}6052RT}{F} \log \left(1 + \frac{2mM}{1000}\right) \text{ by } E_\rho$$

we obtain

$$E + \frac{2RT}{F} \ln m = E_0 + \frac{0{\cdot}1183Am^{\frac{1}{2}}}{1 + \beta a_i m^{\frac{1}{2}}} + E_\rho \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

which on rearrangement gives

$$E - E_\rho + \frac{2RT}{F} \ln m - 0{\cdot}1183Am^{\frac{1}{2}} = E_0 - (E - E_\rho + \frac{2RT}{F} \ln m - E_0)\beta a_i m^{\frac{1}{2}} \quad . \quad (5)$$

A plot of the left-hand side against $[E - E_\rho + (2RT/F) \ln m - E_0]m^{\frac{1}{2}}$ is made, an approximate value of E_0 being assumed from the plots made according to the method of Lewis and Randall, and the approximation is continued until a straight line is obtained and until the value of E_0 given by the intercept at zero concentration equals the value of E_0 assumed. From the slope of the graph, which equals $-\beta a_i$, a_i can be calculated.

Values for the dielectric constant of aqueous glucose mixtures are not reported in the literature but values for aqueous sucrose, mannitol, glycerol, and ethylene glycol mixtures are given by Harned and Owen ("Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., 1943, p. 118), and mixtures containing the same percentage of water by weight show values of dielectric constant very close together. Since these substances contain polar groups similar to those in glucose, we might expect water–glucose mixtures to have dielectric constants of approximately the same values. If this reasoning is correct the dielectric constants (D) of water–glucose mixtures should be approximately as follows: 50% glucose 64·0, 40% glucose 67·5, 32% glucose 70·0, 25% glucose 72·0, 15% glucose 74·8. These values being used for the calculation of A and B in each case, plots were made as described above, and satisfactory straight lines were obtained intercepting the axis at zero concentration at the following values for E_0:

Glucose in solution, %	15	25	32	40	50
E_0, volts	0·2074	0·1964	0·1885	0·1788	0·1634

These values correspond very closely (within $\pm 0{\cdot}1$ mv.) with the values which would be suggested by the plot of $E + (2RT/F) \ln m$ against $m^{\frac{1}{2}}$.

These results therefore suggest that: (*a*) The standard electrode potentials of the silver–silver chloride electrode in water–glucose mixtures are as given above. (*b*) The values of the dielectric constant of water–glucose mixtures are very close to those suggested. (*c*) Because straight lines are obtained, the mean activity coefficients of hydrochloric acid in such solutions are adequately described by equation (3), and the Gronwall, La Mer, and Sandved extension terms (*Physikal. Z.*, 1928, **29**, 358) need not be included even in the solution of lowest dielectric constant considered. This supports Harned and Morrison's statement (*Amer. J. Sci.*, 1937, **33**, 161; *J. Amer. Chem. Soc.*, 1936, **58**, 1908) that in the calculation of activity coefficients of hydrochloric acid in dioxan–water mixtures the Gronwall, La Mer, and Sandved extension terms play a significant part only in solutions of dielectric constant less than 60.

The Mean Activity Coefficients of Hydrochloric Acid in Water–Glucose Mixtures.—Insertion of the values for E_0 given above in equation (2) leads to evaluation of the mean activity coefficients of hydrochloric acid at the various concentrations concerned. These have been evaluated, and from the graphs the values at rounded concentrations are given in the following table, the values for the activity coefficients in pure water, included for comparison, being obtained from Shedlovsky and MacInnes (*J. Amer. Chem. Soc.*, 1936, **58**, 1930).

Mean activity coefficients (reported as $-\log_{10}\gamma_\pm$) *of* HCl *in water–glucose mixtures at* 25°.

	Glucose, %.					
m.	0.	15.	25.	32.	40.	50.
0·1	0·0989	0·1162	0·1188	0·1264	0·1285	0·1345
0·09	—	0·1130	0·1156	0·1223	0·1252	0·1305
0·08	—	0·1094	0·1124	0·1183	0·1212	0·1272
0·07	—	0·1045	0·1076	0·1134	0·1165	0·1216
0·06	—	0·0996	0·1030	0·1078	0·1117	0·1164
0·05	0·0807	0·0936	0·0965	0·1010	0·1046	0·1096
0·04	—	0·0870	0·0898	0·0938	0·1075	0·1030
0·03	—	0·0788	0·0815	0·0846	0·0875	0·0934
0·02	0·0578	0·0675	0·0709	0·0728	0·0752	0·0807
0·01	0·0434	0·0506	0·0521	0·0550	0·0568	0·0612
0·005	0·0323	0·0350	0·0365	0·0324	0·0404	0·0431

The Distance of Closest Approach of Ions.—The slope of the graphs in which $E - E_\rho + (2RT/F) \ln m - 0{\cdot}1183\,Am^{\frac{1}{2}}$ is plotted against $[E - E_\rho + (2RT/F) \ln m - E_0]m^{\frac{1}{2}}$ equals $-\beta a_i$. By using the values of D listed above, values of β have been obtained which lead to the following values for the distance of closest approach of ions:

Glucose solution, %	15	25	32	40	50
Distance of closest approach, A.	4·9	5·3	4·95	5·3	6·2

These values correspond closely to the value of 5·3 A. for hydrochloric acid in water determined by Harned and Ehlers (*J. Amer. Chem. Soc.*, 1932, **54**, 1350), suggesting that the presence of glucose in the solution does not affect the distance of closest approach of ions, and also that the ions are solvated in such mixtures completely by water molecules and that the glucose molecules do not take part in or interfere with such solvation.

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484. *The Conversion of Arylureas into Symmetrical Diarylureas. The Melting Points of Certain Substituted Ureas.*

By FREDERICK KURZER.

The preparation of 1-*ureido*-2- and 1-*ureido*-4-*alkoxynaphthalenes* is described and their conversion into the corresponding symmetrical *bisalkoxynaphthylureas* examined. The conversion into the *s*-diarylureas occurs particularly rapidly in the *para*-substituted series and accounts for the occurrence of indefinite melting points in certain substituted arylureas. The analogous behaviour of 2- and 4-diphenylylureas is also recorded.

THE conversion of arylureas above their melting points into symmetrical diarylureas has often been observed (*e.g.*, Sell, *Annalen*, 1863, **126**, 157). Davis *et al.* (*J. Amer. Chem. Soc.*, 1922, **44**, 2595; 1923, **45**, 1816) showed that arylureas dissociated in two ways, forming on the one hand *iso*cyanic acid and an aromatic amine (equation 1), and on the other ammonia and aryl *iso*cyanate (equation 2); recombination of the aromatic dissociation products according to equation 5 accounted for the production of the symmetrical diarylureas. The thermal rearrangement of 1-aryl-3-alkylureas into symmetrical diarylureas was accounted for similarly (see equations 3—6).

$$\mathrm{Ar{\cdot}NH{\cdot}CO{\cdot}NH_2} \longrightarrow \begin{cases} \mathrm{Ar{\cdot}NH_2 + HNCO} & (1) \\ \mathrm{Ar{\cdot}NCO + NH_3} & (2) \end{cases}$$

$$\mathrm{Ar{\cdot}NH{\cdot}CO{\cdot}NHAlk} \longrightarrow \begin{cases} \mathrm{Ar{\cdot}NH_2 + Alk{\cdot}NCO} & (3) \\ \mathrm{Ar{\cdot}NCO + Alk{\cdot}NH_2} & (4) \end{cases}$$

$$\mathrm{Ar{\cdot}NH_2 + Ar{\cdot}NCO} \longrightarrow \mathrm{Ar{\cdot}NH{\cdot}CO{\cdot}NHAr} \quad (5)$$

$$\mathrm{Alk{\cdot}NH_2 + Alk{\cdot}NCO} \longrightarrow \mathrm{Alk{\cdot}NH{\cdot}CO{\cdot}NHAlk} \quad (6)$$

1-*Ureido*-2- and 4-*ureido*-1-*naphthol* were prepared by existing methods from the corresponding aminonaphthols, and were converted into the *methyl* and *ethyl ethers*. Prolonged fusion of 1-amino-2-naphthol hydrochloride with urea gave *di*-2-*hydroxy*-1-*naphthylurea*, also produced by heating 1-ureido-2-naphthol at 250° for one hour. *Di*-2-*alkoxy*-1-*naphthylureas* were obtained by heating 1-ureido-2-alkoxynaphthalenes above their melting points, or by boiling their aqueous solutions for several hours, and were identical with specimens prepared by the alkylation of di-2-hydroxy-1-naphthylurea. The rearrangement of 1-ureido-4-alkoxynaphthalene to symmetrical *di*-4-*alkoxy*-1-*naphthylureas* at elevated temperatures occurred with particular ease: conversion took place almost instantaneously and was completed by brief heating near the melting point of the starting material.

The ureidoalkoxynaphthalenes described are closely related to the intensely sweet 4-ureidophenetole ("Dulcin"). 1-Ureido-4-methoxy- and 1-ureido-4-ethoxy-naphthalene were found to be tasteless or very faintly bitter probably owing to the change of a benzene for a naphthalene nucleus and to their very limited solubility in water at ordinary temperatures. These results agree with the observation, that introduction of even a single alkyl group into the "Dulcin" molecule (as, for example, in 4-ureido-3-methylphenetole) suppresses the sweet taste. 4-Ureido-1-naphthol, produced, after a bitter, burning sensation, a persistent sweet taste; similar, but very faint effects were observed with the *ortho*-isomer.

The behaviour of arylureas on fusion recalls the frequent discrepancies in the reported melting points of certain urea derivatives, particularly asymmetric aryl-, diaryl-, and arylalkylureas (cf. Beilstein's Handbuch, 1929, **12**, 801, 941, 1292). The decomposition temperature of 4-bromophenylurea, for example, has variously been given at points between 220° and 296° (see experimental). Wheeler (*J. Amer. Chem. Soc.*, 1929, **51**, 3653), although noticing a difference

in the behaviour of this compound on slow and rapid heating, was unable to account for these observations. Van Gelderen (*Rec. Trav. chim.*, 1933, **52**, 976), describing the preparation of a series of substituted *p*-diphenylylureas of the type $Ph{\cdot}C_6H_4{\cdot}NH{\cdot}CO{\cdot}NR'R''$, has pointed out that the melting points of the majority of compounds studied were not sharp, and ascribed this to the changes represented by equations (3—6). The observation that the decomposition ranges of these derivatives depended on the rate of heating, the nature of the melting-point apparatus used, etc., led to the conclusion that melting points cannot be used for the characterisation of substituted ureas.

The results obtained in the present investigation have shown that the thermal conversion of aryl- into the corresponding diaryl-ureas, proceeding according to equations (1), (2), and (5), takes place extremely rapidly, often below the melting point, with arylureas containing certain substituents, particularly in the position *para* to the ureido-group, and is responsible for the occurrence of indefinite melting points. Thus, for example, whilst 2-diphenylylurea melted sharply at 158—160°, 4-diphenylylurea, heated under the same conditions, sintered at 180—190° and re-melted at 295—300°. This behaviour was accounted for by experiments which showed that 4-diphenylylurea was completely converted into bis-4-diphenylylurea, m. p. 316°, by heating at 210° for 10 minutes. The corresponding conversion of the *ortho*-isomer into *bis-2-diphenylylurea*, however, was incomplete after 1 hour's heating; a sample of the melt withdrawn after 10 minutes' fusion showed a nitrogen content corresponding to a mixture of 84% of starting material, and 16% of bis-2-diphenylylurea. On prolonged heating, small quantities of *2-diphenylylbiuret* were obtained in this conversion, but not in the others. The formation of biurets is readily accounted for by the following extension of Davis's mechanism:

$$Ar{\cdot}NH{\cdot}CO{\cdot}NH_2 + HNCO \longrightarrow Ar{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH_2 \quad . \quad . \quad . \quad . \quad . \quad (7)$$

In determining the melting points of substituted ureas which undergo the above rearrangement rapidly it seems desirable to carry out the measurements under such conditions that conversion into the symmetrical diarylurea is avoided as far as possible. Reproducible values have now been determined by the following simple procedure: after the approximate softening temperature or melting range of the urea had been found, the bath temperature of the apparatus was raised 10—20° above that point, and samples inserted into the slowly cooling bath, until a temperature was reached at which a specimen just failed to liquefy. Insertion of another specimen at a temperature one degree higher caused instantaneous fusion, and could be taken as the "melting point" of the urea derivative under examination. Under these conditions, practically no conversion into diarylurea occurs, and samples withdrawn immediately after fusion showed nitrogen contents corresponding to the original arylurea. If left in the melting-point apparatus, the fused arylurea normally resolidified after a few seconds and then showed a second melting point, that of the diarylurea. This procedure gives satisfactorily reproducible physical constants for urea derivatives whose properties preclude slow heating. Using this method it has been found that melting points recorded in the literature for arylureas are indeed often those of the corresponding diarylureas, or mixtures of both. Thus, for example, 4-diphenylylurea melts sharply at 197—198°, whilst the "decomposition temperature," 210°, reported by van Gelderen (*loc. cit.*), is that of a mixture with bis-4-diphenylylurea. Similar considerations apply to the constants recorded by Herrmann (*Annalen*, 1922, **429**, 163) for 1-ureido-4-ethoxynaphthalene ("sintering at 205—207°, decomposition at 264—265°"). The compounnd was found to melt at 221—222°; short heating above this melting point rapidly converted it into *di-4-ethoxy-1-naphthylurea*, m. p. 266—267°. The analogous behaviour of 4-bromophenylurea is also described.

Experimental.

All m.p.s are uncorrected. Analyses are by Drs. Weiler and Strauss. M.p.s of *p*-substituted arylureas were determined by the method described in the theoretical section.

1-*Ureido-2-naphthol*.—(a) *By the action of urea.* 1-Amino-2-naphthol hydrochloride (20 g., 1 mol.), dissolved in a mixture of water (150 ml.) and glacial acetic acid (2 ml.), was treated with urea (40 g., 6·5 mols.) and the whole heated under reflux with mechanical stirring for one hour. After cooling of the solution to room temperature, the product was filtered off and freed from coloured impurities by boiling briefly under reflux with ethanol (40 ml.). The residue in sodium hydroxide solution (500 ml.; 2% w/v), was treated with sodium dithionite (1 g.), and stirred with charcoal at 60° for ½ hour. After the removal of the carbon, the product was precipitated by passage of sulphur dioxide. A second reprecipitation, and cooling to 0°, gave 1-*ureido-2-naphthol* (15—18 g.; 60—72%) in white micro-crystalline plates, m. p. 224—225° (decomp.) (Found: C, 65·4; H, 5·0; N, 13·6. $C_{11}H_{10}O_2N_2$ requires C, 65·35; H, 4·95; N, 13·85%).

(b) *By the action of sodium cyanate.* To a solution of 1-amino-2-naphthol hydrochloride (10 g., 1 mol.) in water (150 ml.) at 30°, sodium cyanate (10 g., 3 mols.; saturated aqueous solution) was added

with stirring. The product separated immediately as a greyish-purple solid. After two reprecipitations with sulphur dioxide 1-ureido-2-naphthol, m. p. 224—225° (decomp.), was obtained as a white microcrystalline powder (8—9 g.; 63—71%) (Found: N, 13·9%). 1-Ureido-2-naphthol is difficultly soluble in hot methanol, ethanol, and acetone, and almost insoluble in benzene and light petroleum. Crystallization from ethanol yields shiny needles, m. p. 225—226° (decomp.).

1-*Ureido*-2-*methoxynaphthalene*.—1-Ureido-2-naphthol (4 g., 1 mol.), dissolved in sodium hydroxide solution (100 ml.; 5% w/v) was treated at 50° with methyl sulphate (12 g., 5 mols.) in two portions. The reaction mixture, from which the crude product separated immediately, was kept at 100° for 30 minutes, and maintained alkaline by the addition of more sodium hydroxide solution. After being cooled to 0° and filtered, the product was crystallized from dilute ethanol (200 ml.; 80%) and gave 1-*ureido*-2-*methoxynaphthalene*, m. p. 236—238°, in colourless lustrous plates (3·5 g.; 75%), which recrystallized from a large volume of boiling water as needles (Found: C, 66·9; H, 5·5; N, 11·8. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 13·0%). Tasteless.

1-*Ureido*-2-*ethoxynaphthalene*.—This *product*, obtained by the procedure used for the methoxy-compound in 60% yield, formed shiny needles, m. p. 194—196° (Found: C, 67·5; H, 6·0; N, 12·2. $C_{13}H_{14}O_2N_2$ requires C, 67·85; H, 6·1; N, 12·2%). It was sparingly soluble in water, producing a faint bitter taste.

1-*Acetamido*-2-*naphthyl Acetate*.—1-Ureido-2-naphthol (6 g., 1 mol.), in pyridine (50 ml.), was heated with acetic anhydride (30 g., 10 mols.) at 100° for two hours. The resulting liquid was poured into water (250 ml.), and well-developed prisms separated overnight (4·5 g.; 60%). After two crystallizations from ethanol (150 ml., 120 ml.) 1-acetamido-2-naphthyl acetate, m. p. 204—206°, was obtained in lustrous colourless prisms (Found: C, 68·7; H, 5·4; N, 5·5, 5·9. Calc. for $C_{14}H_{13}O_3N$: C, 69·1; H, 5·35; N, 5·8%). The m. p. was not depressed on admixture with authentic material (Michel and Grandmougin, *Ber.*, 1892, **25**, 3432). Alkaline hydrolysis gave lustrous plates of 1-acetamido-2-naphthol, m. p. 235—236° (decomp.).

Di-2-*hydroxy*-1-*naphthylurea*.—(a) *From* 1-*amino*-2-*naphthol hydrochloride*. An intimate mixture of 1-amino-2-naphthol hydrochloride (20 g., 1 mol.) and urea (24 g., 4 mols.) was fused at 160° in nitrogen. The temperature of the orange melt was raised slowly and maintained at 200° for 1 hour, while strong evolution of ammonia took place. The solidified product was broken up, and its alkaline solution (4% w/v sodium hydroxide solution) treated at 40° with charcoal, followed by precipitation with sulphur dioxide. After two reprecipitations *di*-2-*hydroxy*-1-*naphthylurea*, m. p. 214—216°, was obtained as a white micro-crystalline powder (14—15 g.; 81—87%) (Found: C, 73·0; H, 4·4; N, 7·9. $C_{21}H_{16}O_3N_2$ requires C, 73·3; H, 4·65; N, 8·1%).

(b) *From* 1-*ureido*-2-*naphthol*. 1-Ureido-2-naphthol (1 g.) was melted and maintained at 240° for 1 hour. Isolation of the product as described above gave di-2-hydroxy-1-naphthylurea (0·75 g.), m. p. 214—215° (Found: N, 8·7%).

Di-2-*methoxy*-1-*naphthylurea*.—(a) *From di*-2-*hydroxy*-1-*naphthylurea*. Treatment of the symmetrical hydroxy-compound with methyl sulphate as previously described (but under somewhat more drastic conditions—80°; 30 minutes' shaking) and two crystallizations from aqueous acetic acid, gave microcrystalline needles of *di*-2-*methoxy*-1-*naphthylurea*, m. p. 268—270° (decomp), in excellent yield (Found: C, 73·8; H, 5·5; N, 7·25. $C_{23}H_{20}O_3N_2$ requires C, 74·2; H, 5·4; N, 7·5%).

(b) *From* 1-*ureido*-2-*methoxynaphthalene*. 1-Ureido-2-methoxynaphthalene (1 g.) was heated under reflux for 2 hours with water (250 ml.), in which it dissolved very gradually. The solution was slowly evaporated to small bulk (50 ml.) during 2 hours and cooled to 0°, and then deposited a product which gave di-2-methoxy-1-naphthylurea (0·5 g.), m. p. 268—270° (decomp.), from aqueous acetic acid. There was no depression of m. p. in admixture with material obtained by method (a) (Found: N, 7·35%).

(c) 1-Ureido-2-methoxynaphthalene (1 g.) was heated above its melting point in nitrogen for 30 minutes; ammonia was evolved and partial re-solidification occurred. Crystallization of the residue from aqueous acetic acid, with the addition of decolorizing carbon, gave di-2-methoxy-1-naphthylurea (0·4 g.), m. p. 268—270° (decomp.) not depressed on admixture with material obtained by method (a) (Found: N, 7·9%).

Di-2-*ethoxy*-1-*naphthylurea* was prepared by methods (a) and (c), and formed colourless needles, m. p. 246—247° (Found: N, 7·3, 7·5. $C_{25}H_{24}O_3N_2$ requires N, 7·0%).

4-*Ureido*-1-*naphthol*.—1-Amino-4-naphthol hydrochloride (10 g., 1 mol.) in water (100 ml.) was added dropwise within 15 minutes, with mechanical stirring, to a solution of sodium cyanate (10 g., 3 mols.) in water (120 ml.), cooled externally to 0°. The temperature of the reaction mixture was kept below 5° by the addition of ice. The pale purple solid obtained was dissolved in sodium hydroxide solution (200 ml.; 2% w/v), treated with charcoal at 50° for 30 minutes, and reprecipitated by the slow addition of excess of dilute sulphuric acid to the filtrate, previously cooled to 0°. After two further reprecipitations, 4-*ureido*-1-*naphthol*, m. p. 184—185° (decomp.), was obtained as a white micro-crystalline powder (8—9 g.; 80—90%) (Found: C, 64·9; H, 4·8; N, 13·3. $C_{11}H_{10}O_2N_2$ requires C, 65·35; H, 4·95; N, 13·85%). It turns pale purple on storage, is readily soluble in methanol, ethanol, and acetone and can be crystallized from ethanol–light petroleum. An aqueous solution of this compound produced, after a bitter burning sensation, a persistent sweet taste. Attempts to prepare 4-ureido-1-naphthol by boiling a solution of 1-amino-4-naphthol hydrochloride with urea failed.

1-*Ureido*-4-*methoxynaphthalene*.—Methylation of 4-ureido-1-naphthol as previously described gave a *product* (72% yield) which crystallized from ethanol–water (2 : 1) as white micro-crystalline needles, m. p. 224—225° (Found: C, 65·95; H, 5·45; N, 12·9. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 13·0%). The compound was very sparingly soluble in water and produced a faint bitter taste.

1-*Ureido*-4-*ethoxynaphthalene*.—This was prepared analogously. It was twice crystallized from ethanol and formed a silky mass of white micro-crystalline needles, m. p. 221—222° (Found: C, 67·6; H, 5·6; N, 11·9. Calc. for $C_{13}H_{14}O_2N_2$: C, 67·85; H, 6·1; N, 12·2%). Herrmann (*loc. cit.*) reports sintering at 205—207°, followed by decomposition at 264—265°. The bitter taste reported by this author for the compound is very faint and appears to be confined to its alcoholic solution.

Di-4-*hydroxy*-1-*naphthylurea*.—A mixture of finely ground 1-amino-4-naphthol hydrochloride (12 g., 1 mol.) and urea (12 g., 3 mols.) was put into a paraffin bath at 250°, and the temperature rapidly raised

to 270°. The vigorous reaction accompanied by evolution of ammonia slackened after 15 minutes and heating was discontinued. The powdered melt (21 g.) was dissolved in warm sodium hydroxide solution (250 ml.; 3% w/v) containing a little sodium dithionite, and purified with charcoal, and the product precipitated from the filtrate at 0° with dilute hydrochloric acid. Two further reprecipitations gave *di-4-hydroxy-1-naphthylurea* as a pale-grey powder, m. p. 208—210° (decomp.) (Found: N, 8·6. $C_{21}H_{16}O_3N_2$ requires N, 8·1%). Fusion of the corresponding unsymmetrical urea derivative above the m. p. was unsuitable for the preparation of this compound.

Di-4-methoxy-1-naphthylurea.—1-Ureido-4-methoxynaphthalene (1 g.), was heated to 240° for 10 minutes. After rapid fusion, the material resolidified immediately and formed a white mass (0·9 g.; m. p. 306—307°), a small specimen of which was crystallized from ethanol and gave white micro-crystalline *di-4-methoxy-1-naphthylurea*, m. p. 310—312° (decomp.) (Found: N, 7·6. $C_{23}H_{20}O_3N_2$ requires N, 7·5%).

Di-4-ethoxy-1-naphthylurea.—This was prepared similarly and formed a micro-crystalline mass, m. p. 276—278° (decomp.) (Found: N, 7·4. $C_{25}H_{24}O_3N_2$ requires N, 7·0%).

Bis-2-diphenylylurea.—2-Diphenylylurea (1 g.) (Morgan and Walls, *J.*, 1932, 2225) was heated to about 200° for 1½ hours. The brown melt began to solidify after ½ hour and had set completely at the end of 1 hour. The powdered material was boiled with three successive portions of ethanol (3 × 20 ml.), giving an insoluble powdery residue of *2-diphenylylbiuret*, m. p. 258—260° (0·2—0·3 g.) (Found: C, 65·6; H, 5·1; N, 16·3, 16·4. $C_{14}H_{13}O_2N_3$ requires C, 65·9; H, 5·1; N, 16·5%). The pale violet filtrates were decolorized with carbon and concentrated to small volume and then deposited clusters of lustrous needles (0·4—0·5 g.) of *bis-2-diphenylylurea*, m. p. 185—186° (Found: N, 7·95. $C_{25}H_{20}ON_2$ requires N, 7·7%).

In separate experiments, 2-diphenylylurea was fused at 200° for 5 and 10 minutes. The melts, which were completely soluble in ethanol (indicating absence of 2-diphenylylbiuret) were finely powdered, and extracted with a little cold water to remove traces of urea. The specimens showed nitrogen contents (12·6 and 12·3%) corresponding to the presence of 90 and 84% of the original unsymmetrical urea, respectively.

Bis-4-diphenylylurea.—4-Diphenylylurea (2·12 g.) (van Gelderen, *loc. cit.*) was maintained at 200—210° for 10 minutes. After 5 minutes, the substance softened and melted partially, but solidified on continued stirring. The cooled material was finely powdered, boiled with ethanol (30 ml.), filtered, and dried (1·6 g.; 87%). Crystallization of a specimen from a large volume of ethanol gave white micro-crystalline bis-4-diphenylylurea, m. p. 316—318° (Found: C, 82·3; H, 5·7; N, 7·65. Calc. for $C_{25}H_{20}ON_2$: C, 82·4; H, 5·5; N, 7·7%).

Di-4-bromophenylurea.—The m. p. of 4-bromophenylurea [reported as approximately 260° (decomp.) (Pinnow, *Ber.*, 1891, **24**, 4172), above 270° (decomp.) (Dains and Wertheim, *J. Amer. Chem. Soc.*, 1920, **42**, 2303), above 265° (decomp.) (Scott and Cohen, *J.*, 1922, **121**, 2034), at 220° or 296° (decomp.) (Wheeler, *J. Amer. Chem. Soc.*, 1929, **51**, 3653), and at 278° (Desai *et al.*, *J.*, 1934, 1186)] was found consistently to be 225—227° when determined by the technique described in this paper. 4-Bromophenylurea (1·5 g.) was heated to 240° for 8 minutes, and the white, amorphous, partially sublimed mass crystallized from glacial acetic acid (250 ml.), yielding lustrous needles of di-4-bromophenylurea, m. p. 314—316° (decomp.) (Found: N, 7·75. Calc. for $C_{13}H_{10}ON_2Br_2$: N, 7·6%). [The following m. p.s have been recorded for this compound: 320—330° (decomp.) (Biltz, *Annalen*, 1909, **368**, 227), 218—219° (Sah *et al.*, *J. Chinese Chem. Soc.*, 1936, **4**, 193), and 275—277° (Zetzsche *et al.*, *Ber.*, 1938, **71**, 1088).]

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485. *Preparation of* spiro*Pyrans Derived from 9-Methyl- and 9-Ethyl-thiaxanthylium and 9-Benzylxanthylium Salts. The Action of Grignard Solutions on Thermochromic* spiro*Pyrans.*

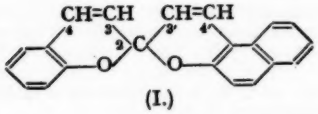
By AHMED MUSTAFA.

(*a*) *spiro*Pyrans (II*a*—II*c*) derived from 9-methyl- and 9-ethyl-thiaxanthylium and 9-benzylxanthylium salts have been prepared. These *spiro*pyrans are compared with benzo-β-naphtho*spiro*dipyran (I).

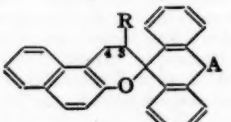
(*b*) The action of various Grignard solutions on thermochromic *spiro*pyrans (II*a* and V) leads to formation of 2 : 3-dihydrofuran derivatives (IV and VI).

(*a*) DICKINSON and HEILBRON (*J.*, 1927, 1699) have shown that only *spiro*pyrans having at least one of the pyran rings attached to a naphthalene nucleus form coloured ions when heated; further, that the 3′-carbon atom in the naphthopyran ring must be unsubstituted (cf. I). A study has now been made of the condensation of 9-methyl- and 9-ethyl-thiaxanthylium chloride and 9-benzylxanthylium chloride with 2-naphthol-1-aldehyde and of the *spiro*pyrans produced on hydrolysis (cf. Irving, *J.*, 1929, 1093), in order to compare the latter compounds with benzo-β-naphtho*spiro*dipyran (I). β-*Naphthothiaxantho*spiro*pyran* (II*a*, A = S) fulfils the above conditions and, as was expected, develops a pink colour when boiled with diphenyl ether and

also when melted; in both cases the colour disappears on cooling. On the other hand, 3-*methyl*-β-*naphthothiaxanthos*spiro*pyran* (II*b*) and 3-*phenyl*-β-*naphthoxanthos*spiro*pyran* (II*c*), which are analogous to 3′-methyl- and 3′-phenyl-benzo-β-naphtho*spiro*dipyran, respectively, fail to give a colour on heating (cf. Mustafa, *Chem. Reviews*, 1948, **43**, 509).



(I.)

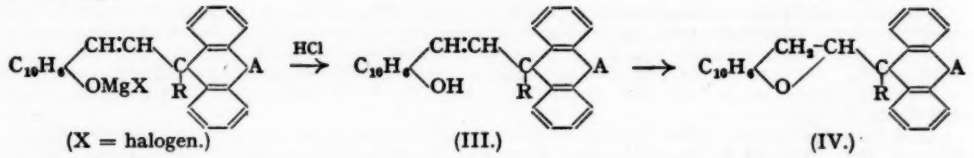


(II*a*; R = H; II*b*; R = Me, A = S; II*c*; R = Ph, A = O.)

The *spiro*pyrans themselves are reconverted into the corresponding thiaxanthylium or xanthylium salts only with difficulty; they give thiaxanthylium and xanthylium salt colorations, not with glacial acetic acid, but only when trichloroacetic acid is used.

(*b*) Recently, Schönberg, Mustafa, and Asker (*J.*, 1947, 847) have investigated the action of Grignard solutions on the thermochromic *spiro*pyrans, followed by hydrolysis, and found that the reaction led to the formation of 2 : 3-dihydrofuran derivatives. This reaction has been further extended, and the action of various Grignard solutions on (II*a*; A = S) and (II*a*; A = O) was studied. Similarly, the reaction leads to the formation of the 2 : 3-dihydrofuran *derivatives*

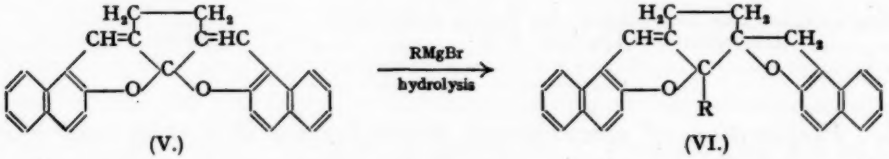
(II*a*) + R·MgX ⟶



(X = halogen.) (III.) (IV.)

(IV) and not of the phenolic compounds (III); (IV; R = Ph, A = S) is insoluble in aqueous alkali solution; it is not attacked by ethereal diazomethane or by benzoyl chloride in the presence of pyridine and is stable towards methyl sulphate in the presence of alkali. The diene reaction of (IV) with maleic anhydride was negative.

Similarly, the action of Grignard solutions on 3 : 3′-ethylenedi-β-naphtho*spiro*dipyran (V) leads to products which show properties analogous to those of (IV; R = Ph, A = S). These compounds are therefore formulated as (VI).



(V.) (VI.)

Experimental.

3-*Phenyl*-β-*naphthoxanthos*spiro*pyran* (II*c*).—To a solution of 9-benzylxanthol (Decker, *Ber.*, 1905, **38**, 2493) (5 g.) in absolute ethyl alcohol (40 c.c.) was added 2-naphthol-1-aldehyde (6 g.), and a slow stream of dry hydrogen chloride gas was introduced. The yellow solution gradually darkened and reddish-brown crystals separated. After standing in the cold for 48 hours, the crystals were filtered off, and a suspension of these in acetone was hydrolysed by means of dilute aqueous ammonia, whereupon the crystals became colourless. The product was separated, washed with water, and crystallised from chloroform–light petroleum (b. p. 30—50°), forming colourless crystals, m. p. 240° (reddish-brown melt) (Found: C, 87·5; H, 4·6. $C_{31}H_{20}O_2$ requires C, 87·7; H, 4·7%). The spiro*pyran* (II*c*) is soluble in hot chloroform, but difficulty soluble in benzene. Its solution in diphenyl ether or tetralin is colourless, and it gives an orange-red colour with green fluorescence when treated with concentrated sulphuric acid.

β-*Naphthothiaxanthos*spiro*pyran* (II*a*, A = S).—The theoretical quantity of 2-naphthol-1-aldehyde (6·5 g.) was added to a dry solution of 9-methylthiaxanthol in ether, prepared from thiaxanthone (10 g.) (Decker, *loc. cit.*), and a slow stream of dry hydrogen chloride gas was introduced. The yellow solution gradually changed to deep red with the separation of crystals, and was kept at 0° for 3 days; the crystals were filtered off, suspended in acetone, and treated with aqueous ammonia solution. The colourless solid obtained was filtered off, boiled with alcohol several times, and finally crystallised twice from benzene–light petroleum (b. p. 30—50°). The spiro*pyran* (II*a*; A = S) formed colourless crystals melting at 230° to a deep red liquid, becoming colourless again on solidification (Found: C, 82·3; H, 4·4; S, 8·5. $C_{25}H_{16}OS$ requires C, 82·4; H, 4·4; S, 8·8%). The solution of the compound in boiling xylene was

colourless, but in boiling diphenyl ether or tetralin, a pink colour was obtained which disappeared on cooling. It gives a deep red colour changing to green after a few minutes when treated with concentrated sulphuric acid. It is difficulty soluble in boiling ethyl alcohol and light petroleum (b. p. 90—100°).

3-*Methyl-β-naphthothiaxanthos*pir*opyran* (II*b*).—Similarly, the theoretical quantity of 2-naphthol-1-aldehyde (6·5 g.) was added to a dry solution of 9-ethylthiaxanthol in ether, prepared from thiaxanthone (10 g.) and ethylmagnesium bromide (24·5 g.) (cf. Irving, *loc. cit.*), and a slow stream of hydrogen chloride was introduced. The yellow solution, which slowly became dark red with the separation of crystals, was kept in the cold for 48 hours; the crystals that separated were filtered off, washed with alcoholic ammonia solution, then with boiling acetone, and finally crystallised from xylene after the addition of light petroleum (b. p. 30—50°), forming colourless crystals, m. p. above 270° (red melt) (Found: C, 82·4; H, 4·5; S, 8·3. $C_{26}H_{18}OS$ requires C, 82·5; H, 4·7; S, 8·4%). The spir*opyran* (II*b*) is soluble in benzene and xylene; its solution in boiling diphenyl ether is colourless and it gives a green solution in concentrated sulphuric acid.

*Action of Grignard Reagents on β-Naphthothiaxanthos*pir*opyran* (II*a*, A = S).—(i) *Phenylmagnesium bromide.* To an ethereal solution of phenylmagnesium bromide (prepared from magnesium, 0·9 g.; bromobenzene, 9 g.; dry ether, 50 c.c.), the *spiro*pyran (II*a*; A = S) (2 g.) and dry benzene (20 c.c.) were added. The mixture was heated under reflux for 2 hours, during which its colour changed from red through green to yellow; it was kept overnight, then decomposed with dilute hydrochloric acid, and extracted with ether. The ethereal solution was dried and evaporated, and the residue, after being washed several times with boiling light petroleum (b. p. 30—50°), was crystallised twice from alcohol, forming colourless crystals, m. p. 152° (colourless melt) [Found: C, 84·0; H, 4·8; S, 6·8; *M* (micro-Rast), 423. $C_{31}H_{22}OS$ requires C, 84·2; H, 5·0; S, 7·2%; *M*, 442]. 9-(2′ : 3′-*Dihydro-β-naphtho-2′-furyl*)-9-*phenylthiaxanthone* (IV; R = Ph, A = S) is readily soluble in benzene and xylene but dissolves with difficulty in light petroleum (b. p. 90—100°). It is insoluble in aqueous sodium hydroxide and dissolves with a pale yellowish-brown colour in concentrated sulphuric acid.

(ii) *Methylmagnesium iodide.* The *methyl* analogue (IV; R = Me, A = S) was similarly obtained by the action of methylmagnesium iodide on (II*a*, A = S) in colourless crystals from methyl alcohol, m. p. 128° (colourless melt) (Found: C, 82·0; H, 5·1; S, 7·9. $C_{26}H_{20}OS$ requires C, 82·1; H, 5·3; S, 8·4%). It is insoluble in aqueous sodium hydroxide and gives a yellow colour when treated with concentrated sulphuric acid.

*Action of Grignard Reagents on β-Naphthoxanthos*pir*opyran* (II*a*, A = O).—(i) *Phenylmagnesium bromide.* The *spiro*pyran (Irving, *loc. cit.*) was treated as described for (II*a*, A = S) with phenylmagnesium bromide. The colour of the reaction mixture changed from yellow to blue and finally pale yellow. The product was decomposed with dilute hydrochloric acid, extracted with ether, and the ether dried, and evaporated. The oily residue, when washed several times with light petroleum (b. p. 30—50°), formed a solid mass which after two crystallisations from benzene–light petroleum (b. p. 90—100°), gave colourless crystals, m. p. 126° (Found: C, 87·0; H, 5·2. $C_{31}H_{22}O_2$ requires C, 87·3; H, 5·2%). 2-(2′ : 3′-*Dihydro-β-naphtho-2′-furyl*)-2-*phenylxanthone* (IV; R = Ph, A = O) dissolves in benzene and hot ethyl alcohol, but is difficultly soluble in light petroleum (b. p. 90—100°) and insoluble in aqueous sodium hydroxide. It dissolves with a yellow colour in concentrated sulphuric acid.

(ii) *Methylmagnesium iodide.* The *methyl* analogue (IV; R = Me, A = O) was obtained by the action of methylmagnesium iodide on (II*a*; A = O) in colourless crystals, m. p. 121° (Found: C, 85·4; H, 5·3. $C_{26}H_{20}O_2$ requires C, 85·7; H, 5·5%), from ethyl alcohol. It is insoluble in aqueous sodium hydroxide, dissolves readily in hot benzene, and gives an orange-yellow colour with concentrated sulphuric acid.

Action of Grignard Reagents on 3 : 3′-*Ethylenedi-β-naphthos*pir*odipyran* (V).—(i) *Phenylmagnesium bromide.* The *spiro*pyran (V) (Heilbron, Heslop, and Irving, *J.*, 1933, 430) (2 g.) was treated with phenylmagnesium bromide (prepared from magnesium, 0·9 g.; bromobenzene, 9·2 g.; dry ether, 50 c.c.) as mentioned above. The product was decomposed with dilute hydrochloric acid and extracted with ether, and the extract dried and evaporated. The crystals so obtained were washed several times with boiling light petroleum (b. p. 30—50°), then with hot benzene, and crystallised from xylene in colourless crystals, m. p. 269° (colourless melt) [Found: C, 87·4; H, 5·1; *M* (micro-Rast), 430. $C_{32}H_{24}O_2$ requires C, 87·6; H, 5·3%; *M*, 452]. 2-(2′ : 3′-*Dihydro-β-naphtho-2′-furyl*)-2-*phenyl*-2′ : 3-*ethylene-β-naphthopyran* (VI; R = Ph) dissolves in hot xylene but is difficultly soluble in boiling ethyl alcohol and ether and is insoluble in aqueous sodium hydroxide. It dissolves with an orange colour in concentrated sulphuric acid.

(ii) *α-Naphthylmagnesium bromide.* The *α-naphthyl* analogue (VI; R = α-$C_{10}H_7$) was obtained by the action of α-naphthylmagnesium bromide (prepared from α-bromonaphthalene, 10·2 g.; magnesium, 1·4 g.; dry ether, 50 c.c.) on (V) (2 g.) in colourless crystals, m. p. 260°, from xylene (Found: C, 88·2; H, 5·0. $C_{37}H_{26}O_2$ requires C, 88·4; H, 5·2%). It is insoluble in aqueous sodium hydroxide, dissolves in hot xylene, but with difficulty in ethyl alcohol, and gives a red colour with concentrated sulphuric acid.

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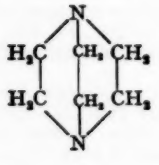
486. *Triethylenediamine* (1 : 4-*Diaza*bicyclo[2 : 2 : 2]*octane*) *and Hexaethylenetetramine. Part I. Synthesis and Properties.*

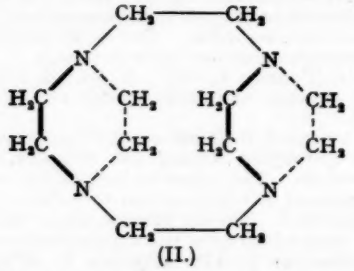
By Frederick G. Mann and Deb. P. Mukherjee.

Dimethylamine in methanol solution reacts with 2 : 2′ : 2″-trichlorotriethylamine monohydrochloride at 125° to form 4 : 4-dimethyl-1-2′-dimethylaminoethylpiperazinium chloride, the hydrochloride of which decomposes at 280—290° to give the hydrochlorides of triethylenediamine and hexaethylenetetramine. These amines can be separated by fractional crystallisation of their picrates. Their identity has been determined by molecular-weight determination on their quaternary methobromides. The dimethobromide of triethylenediamine can also be readily prepared by the union of ethylene dibromide and 1 : 4-dimethylpiperazine.

Triethylenediamine (1 : 4-diaza*bicyclo*[2 : 2 : 2]octane) (I) is a compound of considerable interest for various reasons, in particular for its stereochemical features, its relationship to quinuclidine, and its possible therapeutic properties. Hofmann (*Proc. Roy. Soc.*, 1859, **9**, 153) first claimed to have isolated this diamine, as one of the by-products of the interaction of ethylene dibromide and ammonia (cf. Mann, *J.*, 1934, 461). Harries later asserted (*Annalen*, 1897, **294**, 350) that Hofmann's compound was actually hexaethylenetetramine (1 : 4 : 7 : 10-tetraaza*tricyclo*[8 : 2 : 2 : $2^{4,7}$]hexadecane) (II), although he adduced no evidence in support of his



(I.)



(II.)

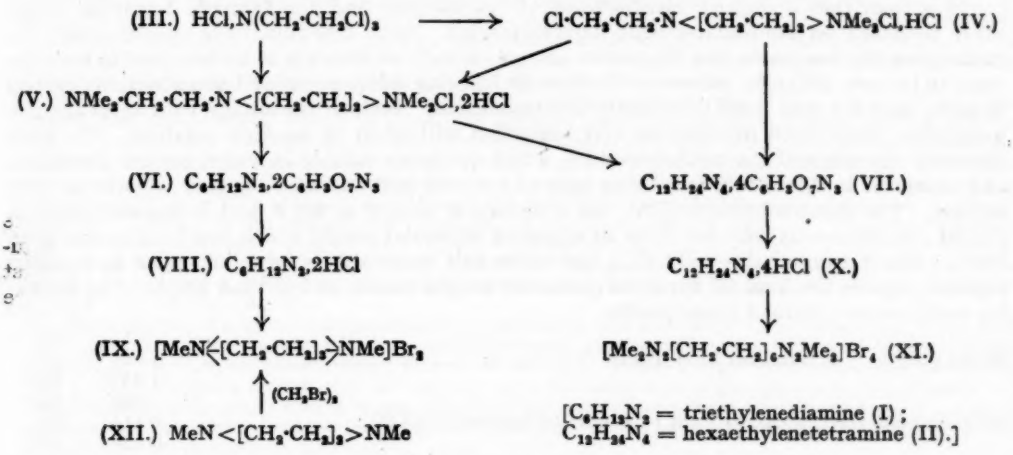
assertion. It should be noted, however, that this tetramine should possess a strainless ring system and hence presumably considerable stability. The configuration of this ring system is shown in (II), where the two piperazine rings are represented as being at right angles to the plane of the paper, so that the bonds shown as heavy and as broken lines are respectively above and below this plane, whereas those shown by normal lines are in the plane of the paper; if the piperazine ring is effectively planar, the normal intervalency angle of 3-covalent nitrogen (*ca.* 110°) could thus be retained.

Mann and Pope (*Proc. Roy. Soc.*, 1925, *A*, **109**, 450) failed to detect the diamine (I) in the products of the thermal decomposition of 2 : 2′ : 2″-triaminotriethylamine trihydrochloride, $N(CH_2{\cdot}CH_2{\cdot}NH_2,HCl)_3$, whilst Prelog, Cerkovnikov, and Ustricev (*Annalen*, 1938, **535**, 37) were unable to synthesise it by the action of sodium hydroxide on 1-2′-bromoethylpiperazine.

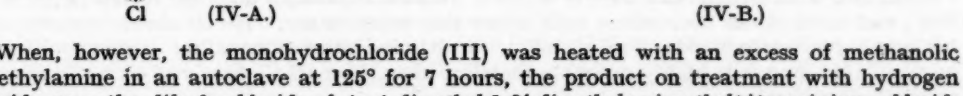
Hromatka (*Ber.*, 1942, **75**, 1302) has claimed to have prepared the diamine (I) in 2% yield by the thermal decomposition of 2 : 2′-dihydroxydiethylamine hydrochloride. His identification of the base as the diamine (I) rests on a molecular-weight determination of its *p*-nitrophenoxide in molten camphor, and of the highly deliquescent free base in xylene by the vapour-pressure method. The nitrophenoxide, as would be expected, underwent considerable dissociation in molten camphor and gave an apparent molecular weight of 144, whereas the undissociated salt of the diamine (I) has the value 390·4; the free base in xylene gave values of 124, 112, 99, and 101, whereas the diamine (I) requires 112·2. Hromatka and Engel (*Ber.*, 1943, **76**, 712) obtained the same base in 25·5% yield by the thermal decomposition of 1-2′-bromoethylpiperazine dihydrobromide, in 22·5% yield by the similar decomposition of 1-2′-chloroethylpiperazine dihydrochloride, and in 2·8% yield by the decomposition of 1-2′-hydroxyethylpiperazine dihydrochloride. Since the weight of the salts used in these experiments ranged only from 0·1 to 0·56 g., the accuracy of the yields claimed is doubtful, particularly as the required diamine (I) had usually to be separated from piperazine which was formed simultaneously.

We have developed a synthesis by means of which salts of both the diamine (I) and the tetramine (II) can be readily isolated in good yield. When 2 : 2′ : 2″-trichlorotriethylamine monohydrochloride (III) was heated with an excess of 40% methanolic dimethylamine at 40—45° for 1·5 hours in a pressure bottle, and the product subsequently treated with hydrogen chloride, the *hydrochloride* of 4 : 4-*dimethyl*-1-2′-*chloroethylpiperazinium chloride* (IV), m. p. 218°,

was obtained. The fact that this product has the constitution (IV) and is not the isomeric hydrochloride of 1 : 4-dimethyl-1-2′-chloroethylpiperazinium chloride (IV-A) is shown both



by the method of preparation and by the fact that a methanolic solution of the compound when shaken with an excess of silver oxide, filtered, and then treated with an excess of cold methyl iodide yielded 4 : 4-*dimethyl*-1-2′-*chloroethylpiperazinium iodide* (IV-B); in this compound, the 1-nitrogen atom is deactivated by the combined electronic attraction of the positively charged $N_{(4)}$ and of the 2′-chlorine atom (cf. Mann and Watson, *J. Org. Chem.*, 1948, **13**, 502). If, however, the hydrochloride had had the structure (IV-A) instead of (IV), the cold methyl iodide would almost certainly have yielded a dimethiodide instead of the monomethiodide (IV-B).



When, however, the monohydrochloride (III) was heated with an excess of methanolic dimethylamine in an autoclave at 125° for 7 hours, the product on treatment with hydrogen chloride gave the *dihydrochloride* of 4 : 4-*dimethyl*-1-2′-*dimethylaminoethylpiperazinium chloride* (V), m. p. 225°. It is therefore highly probable (although not certain) that the chloroethyl compound (IV) is an intermediate in the formation of the dimethylaminoethyl compound (V); since however only the latter was of major importance in our synthesis it was always prepared directly from the monohydrochloride (III).

The dihydrochloride (V), when heated at 280—290°, underwent smooth decomposition with the evolution of basic vapours, and when decomposition was complete the molten residue gave on cooling a brown glass. The latter, consisting of crude amine hydrochlorides, when dissolved in ethanol and treated with ethanolic picric acid gave a copious precipitate whence fractional recrystallisation ultimately furnished *triethylenediamine dipicrate* (VI), m. p. 298°, and *hexaethylenetetramine tetrapicrate* (VII), m. p. 277° (the identification of these isomeric products is described later). The chloroethyl compound (IV), when subjected similarly to thermal decomposition, ultimately gave the tetrapicrate (VII); however, this experiment was conducted on only a small scale, and the existence of the isomeric diamine salt may have escaped detection.

The diamine dipicrate (VI) was converted into the corresponding *dihydrochloride* (VIII), m. p. 290°, and a methanolic solution of this salt was treated with silver oxide, filtered, and then heated with an excess of methyl bromide at 100° in a sealed tube; *triethylenediamine dimethobromide* (IX), m. p. 335°, was obtained.

The tetrapicrate (VII) was similarly converted into the *tetrahydrochloride* (X), m. p. 291°, but the isolation of this very hygroscopic salt in the pure state was difficult and wasteful. Its methanolic solution when treated as above readily gave crystalline *hexaethylenetetramine tetramethobromide* (XI), m. p. 320°.

An alternative synthesis of quaternary salts of the diamine series has also been developed. When 1 : 4-dimethylpiperazine (XII) was heated under suitable conditions with ethylene dibromide, the product readily yielded the dimethobromide (IX) in high yield, and this compound can thus be prepared in quantity. We have some evidence that in this condensation a small

proportion of the isomeric tetramethobromide (XI) may also be formed, but the isolation of pure derivatives of the tetra-amine series involves repeated recrystallisation and is not a practicable synthesis by this route.

It is clear that a decisive identification of the diamine and the isomeric tetramine series must be based on molecular-weight determinations. Such determinations should ideally be made upon the free bases, but Hromatka (*loc. cit.*) found the isolation of his free base in the pure state to be very difficult; moreover the base itself, being deliquescent and also absorbing carbon dioxide, does not lend itself to accurate determinations. Salts of the amines with acids are also unsuitable, since both dissociation and ionisation will occur in aqueous solution. We have therefore investigated the methobromides, which are freely soluble in water, cannot dissociate, and moreover in dilute solution, being salts of a strong acid and a strong base, should be fully ionised. The dimethobromide (IX), has a molecular weight of 301·9, and in aqueous solution should give three ions and thus show an apparent molecular weight which could not be less than 100·6. The tetramethobromide (XI) has twice this molecular weight but, since in aqueous solution it gives five ions, its apparent molecular weight cannot be less than 120·8. The following results were obtained cryscopically.

	*c.**	*M.*
Methobromide (IX) obtained from picrate (VI)	1·076	110
	1·333	108
	1·980	105
Methobromide (IX), obtained from 1 : 4-dimethylpiperazine (XII)	0·414	102
	0·622	105
Methobromide (XI), obtained from picrate (VII), first sample (cf. p. 2302)	1·500	121
	1·726	123
	2·250	127
second sample	1·138	125
	1·474	126
	2·241	128

* G. of solute per 100 g. of water.

These results leave little doubt that (IX) is the dimethobromide, and that (XI) is the tetrabromide, and it is on the basis of these results that the formulæ on p. 2299 have been allocated. Comparison with Hromatka's base is difficult, because Hromatka does not record m. p.s above 280°, and most of our derivatives melt above this temperature. He obtained, however, from his base a *p*-nitrophenoxide of m. p. 183°; our diamine gives a crystalline di-*p*-nitrophenoxide of m. p. 182°, and it is highly probable therefore that Hromatka's base was correctly regarded as triethylenediamine.

This work is now being extended, in particular to the study of the substitution derivatives of the diamine and tetramine.

Experimental.

Many of the salts obtained in this investigation were highly hygroscopic, and considerable care was necessary therefore in their analysis and in the determination of their m. p.s.

2 : 2′ : 2″-*Trichlorotriethylamine Hydrochloride* (III).—This salt was prepared from triethanolamine by the method of McCombie and Purdie (*J.*, 1935, 1217).

4 : 4-*Dimethyl*-1-2′-*chloroethylpiperazinium Chloride Hydrochloride* (IV).—A mixture of the above hydrochloride (III) (7·5 g.) and methanol (12 c.c.) containing 40% of dimethylamine was heated in a pressure bottle at 40—45° for 1·5 hours. Hydrogen chloride was passed into the cold solution to precipitate the *hydrochloride* (IV), which after recrystallisation from ethanol containing a few drops of concentrated hydrochloric acid formed colourless crystals, m. p. 218° (decomp.) (Found: C, 38·6; H, 7·9; N, 11·0. $C_8H_{18}N_2Cl_2,HCl$ requires C, 38·5; H, 7·7; N, 11·3%). The hygroscopic nature of the crude salt diminished markedly on recrystallisation.

A solution of this salt (1 g.) in methanol (15 c.c.) was shaken with silver oxide (2 g.), filtered, mixed with methyl iodide (3 g.), and set aside. The residue after crystallisation from ethanol containing 20% of water gave colourless crystals of 4 : 4-*dimethyl*-1-2′-*chloroethylpiperazinium iodide monohydrate* (IV-B), m. p. 302—305° (decomp.) (Found: C, 29·4; H, 5·7; N, 8·1. $C_8H_{18}N_2ClI,H_2O$ requires C, 29·7; H, 6·2; N, 8·6%); dehydration at 150°/2 mm. gave the anhydrous *iodide* (Found: C, 31·3; H, 6·2; N, 8·9. $C_8H_{18}N_2ClI$ requires C, 31·5; H, 6·0; N, 9·2%).

4 : 4-*Dimethyl*-1-2′-*dimethylaminoethylpiperazinium Chloride Dihydrochloride* (V).—A mixture of the monohydrochloride (III) (75 g.) and 40% methanolic dimethylamine (460 c.c.) was heated in a rotating autoclave for 7 hours at 125°. The cold product was saturated with hydrogen chloride. The precipitated material, when recrystallised from anhydrous ethanol and then thoroughly dried, gave the *dihydrochloride* (V) as colourless hygroscopic crystals, m. p. 225° (decomp.) (73 g., 84%) (Found: C, 39·5; H, 8·95; N, 14·2; Cl, 36·25. $C_{10}H_{24}N_3Cl,2HCl$ requires C, 40·7; H, 8·9; N, 14·2; Cl, 36·1%). Recrystallisation from aqueous ethanol gave the *monohydrate* (Found: C, 38·6; H, 9·2; N, 13·0. $C_{10}H_{24}N_3Cl,2HCl,H_2O$, requires C, 38·4; H, 9·0; N, 13·4%).

A portion of this salt (2·5 g.) was shaken with saturated aqueous potassium hydroxide (2 c.c.) and ether (10 c.c.). The ethereal extract was mixed with methyl iodide, heated under reflux for 30 minutes,

and then evaporated. Recrystallisation of the residue from aqueous ethanol gave 4 : 4-*dimethyl*-1-2′-*dimethylaminoethylpiperazinium iodide methiodide*, m. p. 312° (decomp.) (Found : C, 28·7; H, 5·8; N, 9·4; I, 55·4. $C_{11}H_{27}N_3I_2$ requires C, 28·8; H, 5·9; N, 9·2; I, 55·6%). The same compound was obtained when a methanolic solution of the salt was treated in turn with silver oxide and with cold methyl iodide. It is probable that the second methyl iodide residue in this salt is combined with the 2′-dimethylamino-group, and the salt has the formula $[Me_2N{\cdot}CH_2{\cdot}CH_2{\cdot}N<[CH_2{\cdot}CH_2]_2>NMe_2]I_2$; the strong inductive effect of the positive poles on the two outer quaternary nitrogen atoms would then deactivate the central tertiary nitrogen atom (cf. Mann and Watson, *loc. cit.*).

Thermal Decomposition of the Dihydrochloride (V).—The dihydrochloride (15 g.), contained in a flask carrying an air-condenser closed by a calcium chloride tube, was heated in a metal-bath to 280° and maintained at this temperature for 45 minutes, whereafter the evaporation of volatile material had ceased. The temperature was then dropped to 250° for 30 minutes (to lessen the risk that the required products might themselves slowly decompose), and the product then allowed to cool. The brown glass was dissolved in boiling ethanol (30 c.c.), and the solution when cold filtered to remove a small dark deposit. The filtrate was treated with saturated ethanol picric acid (*ca.* 250 c.c.). The crude yellowish-green picrate (17 g.) was extracted with boiling water containing 5% of ethanol. The filtrate deposited the *tetrapicrate* (VII) which after repeated crystallisation from water containing 30% of ethanol formed yellow crystals, m. p. 277° (decomp.) (Found : C, 38·1; H, 3·2; N, 19·7. $C_{18}H_{24}N_4,4C_6H_3O_7N_3$ requires C, 37·9; H, 3·2; N, 19·6%).

The undissolved residue from the above aqueous extraction was recrystallised repeatedly from glacial acetic acid, and the *dipicrate* (VI), m. p. 298° (decomp.), obtained (Found : C, 37·95; H, 3·2; N, 19·6. $C_6H_{12}N_2,2C_6H_3O_7N_3$ requires C, 37·9; H, 3·2; N, 19·6%). These crystals, even when analytically pure, had a yellowish-green colour, the tint varying with the individual preparation; recrystallisation of a small sample from much boiling water (charcoal) gave a yellow sample of unchanged m. p., but this process was not adopted on the larger scale. A mixture of the picrates (VII) and (VI) had m. p. 257° (decomp.) with preliminary softening.

Thermal Decomposition of the Monohydrochloride (IV).—The hydrochloride (2·5 g.) was heated as above at 270° for 20 minutes. The cold residue was extracted with boiling ethanol (50 c.c.), and the extract treated with saturated ethanolic picric acid. The crude precipitated picrate (2·0 g.) was recrystallised from water containing 30% of ethanol and ultimately furnished the pure tetrapicrate (VII), m. p. 277° (decomp.), unchanged by admixture with that obtained above (Found : C, 38·3; H, 3·7; N, 19·7%).

Derivatives of Triethylenediamine.—Dihydrochloride (VIII). The dipicrate (VI) was thoroughly shaken with an excess of 15% hydrochloric acid, and the product then repeatedly extracted with ether until the aqueous solution was almost colourless. The latter was then evaporated in a desiccator, and the residue, when twice recrystallised from absolute ethanol, gave colourless hygroscopic crystals of the *dihydrochloride* (VIII), m. p. 290° (decomp.) (Found : C, 39·4; H, 8·1; N, 15·3. $C_6H_{12}N_2,2HCl$ requires C, 38·9; H, 7·6; N, 15·1%).

Dimethobromide (IX).—(a) *From the dihydrochloride* (VIII). A solution of the dihydrochloride (VIII) (1 g.) in methanol (20 c.c.) to which water (0·5 c.c.) had been added was shaken with silver oxide (1·5 g.), filtered, transferred to a Carius tube, and chilled to −5°. Methyl bromide (5 g.), also cooled to −5°, was then added, and the sealed tube heated at 80° for 6 hours (although the reaction appeared to be rapid). The contents of several tubes were then united and evaporated in a desiccator. The residue, after recrystallisation from ethanol to which a few drops of water had been added to increase the solvent action, gave the pure *dimethobromide* (IX) as colourless crystals, m. p. 334° (decomp.) (Found : C, 31·4; H, 6·0; N, 9·5; Br, 52·3. $C_8H_{18}N_2Br_2$ requires C, 31·8; H, 6·0; N, 9·3; Br, 52·9%).

Ethanolic solutions of this dimethobromide and of sodium picrate were mixed, and the precipitated *dimethopicrate* was collected, washed with water, and recrystallised from boiling ethanol, in which it was only sparingly soluble : it formed yellow crystals, m. p. 330° (decomp.) (Found : C, 40·5; H, 3·45; N, 19·3. $C_{20}H_{22}O_{14}N_8$ requires C, 40·1; H, 3·7; N, 18·8%).

(b) *From* 1 : 4-*dimethylpiperazine* (XII). A mixture of 1 : 4-dimethylpiperazine (8·3 g.) and ethylene dibromide (13·65 g., 1 mol.), each freshly distilled, was heated in a flask fitted with a reflux air-condenser, slowly to 140°. The faint turbidity which appeared at room temperature gradually became more prominent, and the crystalline salt started to separate at 90—95°, causing considerable "bumping." After the temperature had been maintained at 140° for 1·5 hours, it was reduced to 125° for a further 2 hours, and the solid product then allowed to cool. The pulverised product was thoroughly extracted with cold ethanol (50 c.c.), and the extract filtered and set aside (see below). The undissolved residue was thrice recrystallised from ethanol containing traces of water, and the dimethobromide (16·8 g., 77%) thus obtained as colourless crystals, m. p. 335° (decomp.), unchanged by admixture with that prepared by method (a) [Found : C, 31·4; H, 6·3; N, 9·0; Br (ionic) 52·5%]. This salt also gave the dimethopicrate, m. p. 331° (decomp.), unchanged by admixture with the previous preparation (Found : N, 19·1%).

The cold ethanolic extract of the above crude product was treated with ethanolic sodium picrate, and the precipitated methopicrate, when once recrystallised from ethanol containing a trace of water, had m. p. 238° (decomp.) and when twice recrystallised had m. p. 252° (decomp.); its composition was then that of a pure methopicrate (Found : C, 40·1; H, 3·5; N, 19·2%). Further recrystallisation from ethanol containing 20% of water (to increase the solubility of the picrate) caused however the following changes : (3) m. p. not recorded, (4) 262—268°, (5) 279—280°, (6) 286—287°, (7) 293—294°, (8) 296—297°, (9) 296—297° (all with decomp.). The product after 9 recrystallisations had the same m. p. (mixed and unmixed), and the same composition, as the monoethanolate of the tetramethopicrate (see p. 2302) (Found : H, 4·1; N, 17·6%. Consistent values for carbon could not be obtained). It differed however in that even after the ninth recrystallisation it softened and became slightly brown at *ca.* 10—15° below its m. p., whereas this behaviour was not shown by the product prepared directly from the authentic tetramethobromide.

It is noteworthy that the above combination of 1 : 4-dimethylpiperazine and ethylene dibromide is

considerably inhibited by traces of solvents (*e.g.*, ether), or by even a small excess of the dibromide. Hence the necessity to use correct quantities of the pure reagents.

The molecular weights of the dimethobromide prepared by methods (a) and (b) are recorded on p. 2300.

Di-p-nitrophenoxide. Solutions of the dihydrochloride (VIII) (0·2684 g.) and of sodium *p*-nitrophenoxide (0·5915 g., 2 mols.), each in aqueous ethanol, were mixed and evaporated to dryness in a desiccator. The residue, when recrystallised from ether, gave yellow crystals of the di-*p*-nitrophenoxide, m. p. 182° (Found: N, 14·6. Calc. for $C_6H_{12}N_2,2C_6H_5O_3N$: N, 14·4%). Hromatka (*loc. cit.*) gives m. p. 183°.

Derivatives of Hexaethylenetetramine.—Tetrahydrochloride (X). The tetrapicrate (VII) was decomposed with hydrochloric acid, precisely as was (VI), and the aqueous solution evaporated in a desiccator to a white pasty mass. Recrystallisation of this salt proved difficult and very wasteful as it separated as an oil from all but very dilute solutions. A small quantity of the white crystalline hygroscopic *tetrahydrochloride* (X), m. p. 291° (decomp.), was however obtained from absolute ethanol (Found: C, 38·7; H, 7·5; N, 15·0. $C_{12}H_{24}N_4,4HCl$ requires C, 38·9; H, 7·6; N, 15·1%). A mixture of (X) with the dihydrochloride (VI) had m. p. 241—242°.

Tetramethobromide (XI). The pasty mass of unrecrystallised tetrahydrochloride was dissolved in methanol and treated with silver oxide and methyl bromide precisely as for the dimethobromide (IX). The dried residue, when recrystallised from methanol containing a few drops of water, gave the *tetramethobromide monohydrate* (XI), white crystals, m. p. 309—310° (decomp.) (Found: C, 31·1; H, 6·2; N, 8·4. $C_{16}H_{36}N_4Br_4,H_2O$ requires C, 30·9; H, 6·2; N, 8·9%). This material, when dried at 120°/0·1 mm., gave the anhydrous *salt* (XI), m. p. 320° (decomp.) (Found: C, 31·7; H, 6·3; N, 9·0. $C_{16}H_{36}N_4Br_4$ requires C, 31·8; H, 6·0; N, 9·3%). In the table of molecular-weight determinations (p. 2300), the values for the first sample were obtained using the monohydrate (the concentrations having been calculated for the anhydrous salt), whereas those for the second sample were determined using the anhydrous salt itself.

A solution of this tetramethobromide in ethanol containing a small quantity of water was treated with alcoholic sodium picrate solution. The precipitated yellow *tetramethopicrate*, when collected, washed with water, and recrystallised from ethanol, separated as the crystalline *monoethanolate*, m. p. 298° (Found: C, 40·8; H, 4·5; N, 17·8. $C_{40}H_{44}O_{22}N_{16},C_2H_6O$ requires C, 40·6; H, 4·1; N, 18·0%); the latter, when dried at 150°/2 mm., gave the ethanol-free tetramethopicrate of unchanged m. p. (Found: N, 18·6. $C_{40}H_{44}O_{22}N_{16}$ requires N, 18·8%). A mixture of this compound and the dipicrate (VI), which have the same m. p., had m. p. 258—259°.

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487. *Experiments on the Synthesis of Purine Nucleosides. Part XXIV.* 9-D-*Galactosido*-2-*methylthioadenines.*

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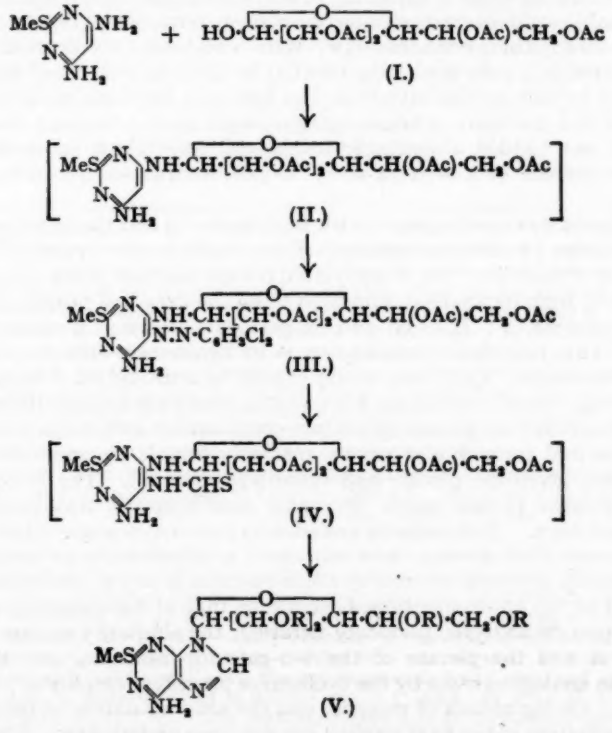
9-D-*Galactopyranosido*-2-*methylthioadenine* has been synthesised by the general method developed in earlier papers of this series. Condensation of 2 : 3 : 5 : 6-tetra-acetyl D-galactofuranose with 4 : 6-diamino-2-methylthiopyrimidine, followed by coupling with diazotised 2 : 5-dichloroaniline, reduction, thioformylation, and cyclisation under conditions which avoided at all stages removal of acetyl groups, yielded a resinous acetylated purine glycoside. Deacetylation of this, followed by treatment with picric acid, yielded 9-D-*galactofuranosido*-2-*methylthioadenine picrate.*

THE general procedure for purine nucleoside synthesis developed in early papers of this series gave rise, in general, to pyranosides when the initial step was direct condensation of an unsubstituted aldose with a suitable 4 : 6-diaminopyrimidine. Various modifications of this step were investigated which might yield 6-amino-4-glycofuranosidaminopyrimidines from which, by normal methods, the furanose forms of the purine nucleosides might be synthesised. The most immediately obvious method in the pentose series—condensation of a 5-acylpentofuranose with a 4 : 6-diaminopyrimidine—failed to yield the desired product. As has already been reported (Kenner, Lythgoe and Todd, Part XVII, *J.*, 1948, 957), the possibility that this failure might have been due to too high reactivity of the furanose sugar caused us to investigate the condensation of a fully acetylated furanose sugar, and 2 : 3 : 5 : 6-tetra-acetyl D-galactofuranose was selected as a model compound. This compound condensed with some difficulty with 4 : 6-diamino-2-methylthiopyrimidine and furnished a product which, when deacetylated and coupled with diazotised 2 : 5-dichloroaniline, gave an azo-glycoside. The latter product on acetylation gave a 6-amino-4-(tetra-acetyl D-galactosidamino)-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine, which differed in its properties from the corresponding pyranose compound and was therefore believed to be a furanoside. Although it clearly indicated a possible route to purine furanosides, this observation was not immediately followed up, largely because another route based on condensation of an *aldehydo*-sugar with a 4 : 6-diaminopyrimidine to yield a Schiff base appeared more promising. The development of the latter method and its final application to the synthesis of adenosine has formed the subject of previous papers (Kenner,

Lythgoe, and Todd, *loc. cit.*; Kenner, Rodda, and Todd, this vol., p. 1613; Kenner, Taylor, and Todd, *ibid.*, p. 1620). It was, however, decided that the route employing acylated furanose sugars, although unlikely to be of preparative value, should be, in due course, explored, and we have therefore studied its application to the synthesis of 9-D-galactofuranosido-2-methylthioadenine.

As a preliminary, the synthesis of 9-D-*galactopyranosido-2-methylthioadenine* was carried out by our general procedure, partly to have available the intermediate and final products for comparison with the corresponding furanose compounds and partly so that the intermediates might be used as model substances in studying any variation of reaction conditions which the lesser stability of the furanose might necessitate at any step in the projected synthesis; the latter point was of some importance in view of the comparative difficulty of obtaining 2 : 3 : 5 : 6-tetra-acetyl D-galactofuranose in large quantity. 6-Amino-4-(tetra-acetyl D-galactopyranosidamino)-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine (Kenner, Lythgoe, and Todd, *loc. cit.*) was reduced with zinc dust and acetic acid, and the product thioformylated. The 6-*amino*-4-(*tetra-acetyl* D-*galactopyranosidamino*)-5-*thioformamido-2-methylthiopyrimidine* so obtained was cyclised with sodium methoxide giving 9-D-galactopyranosido-2-methylthioadenine. The pyranose nature of the product was confirmed by periodate titration, the consumption of oxidant being 3·08 mols. per mol., of which 1 mol. was used up in oxidising the methylthio-group to a methylsulphinyl group (cf. Howard, Lythgoe, and Todd, *J.*, 1945, 556).

In Part XVII (*loc. cit.*) the product (II) obtained by condensing 2 : 3 : 5 : 6-tetra-acetyl D-galactofuranose (I) with 4 : 6-diamino-2-methylthiopyrimidine was deacetylated before coupling



with diazotised 2 : 5-dichloroaniline to form an azo-glycoside. This procedure, although dangerous because of possible furanose–pyranose interconversion in the acetyl-free glycoside, was adopted at the time because the separation of sugar-free azo-compound from the acetylated azo-glycoside had been virtually impossible by the standard chromatographic method hitherto used in such cases. Further work on the Schiff-base route to purine furanosides (Part XXII, *loc. cit.*), however, indicated that furanose–pyranose interconversion under these conditions was almost certain to occur and that the homogeneity of the " azo-galactofuranoside " described in Part XVII (*loc. cit.*) was accordingly doubtful. It was therefore decided that, to ensure retention of a furanose structure, deacetylation must be avoided at all costs until the glyoxaline ring of the

purine system was closed. On the basis of a series of model experiments on the more accessible pyranose azo-galactoside, a suitable chromatographic method, using neutral alumina as adsorbent and toluene as eluting agent to remove sugar-free material, was devised. By its use 6-*amino*-4-(*tetra-acetyl* D-*galactofuranosidamino*)-5-(2′ : 5′-*dichlorobenzeneazo*)-2-*methylthiopyrimidine* (III) was prepared from the initial crude condensation product without removal of acetyl groups at any stage; this furanose azo-glycoside was entirely different in its rotation and solubility from its pyranose isomer. As expected, it differed also from the product obtained when deacetylation preceded formation of the azo-linkage; the product so obtained (Part XVII, *loc. cit.*) must clearly have been a mixture containing much pyranose material.

Reduction of the acetylated azofuranoside with zinc dust in acetic acid, followed by thioformylation of the unstable amino-compound with precipitated dithioformic acid, gave only low yields of acetylated thioformamido-glycoside accompanied by much sugar-free material. As it was thought that the prolonged boiling with dithioformic acid might be a major factor in producing sugar-free material, model experiments were initiated to find some other thioformylation procedure. Sodium dithioformate gave unsatisfactory results and, rather surprisingly, methyl dithioformate (Levi, *Atti R. Accad. Lincei*, **1929**, **9**, 170) did not act as a thioformylating agent; this may have been due to the fact that the ester, a high-melting solid, is polymeric. On the other hand, addition of the calculated amount of acetic acid to methanolic sodium dithioformate at 0° liberated dithioformic acid, apparently as monomer, since it remained almost wholly in solution and was precipitated only when the solution was boiled; this solution of dithioformic acid effectively thioformylates amines at room temperature. By reducing the azo-furanoside with zinc dust and a minimum of acetic acid and thioformylating the product by this method, reasonable yields of crude resinous 6-amino-4-(tetra-acetyl D-galactofuranosidamino)-5-thioformamido-2-methylthiopyrimidine (IV) were obtained. Cyclisation of this product, which was not isolated in a pure state, was effected by heating with fused potassium acetate in acetonitrile solution so that no deacetylation, and hence no furanose–pyranose interconversion, would occur during the reaction. Chromatography then gave a resinous fraction which could not be crystallised but yielded a sparingly soluble *picrate*. From its analysis this material appeared to be the picrate of a 9-(tetra-acetyl D-galactofuranosido)-2-methylthioadenine (V; R = Ac).

The whole synthesis was now repeated with fresh material and the crude cyclisation product split into three fractions by chromatography. Each fraction was separately deacetylated, but the products did not crystallise. The deacetylated middle fraction, however, yielded a sparingly soluble picrate which, from its analysis, appeared to be the expected *picrate* of 9-D-galactofuranosido-2-methylthioadenine (V; R = H) and on periodate titration it consumed 6·38 mols. of oxidant per mol. This periodate consumption is in agreement with the formulation of the product as a hexofuranoside, which one would expect to consume *ca.* 6 mols. of periodate per mol. Under precisely similar conditions 9-D-galactopyranosido-2-methylthioadenine formed a sparingly soluble, but different, picrate (periodate consumption 3·06 mols. per mol.).

The deacetylated first fraction also gave a sparingly soluble picrate which was evidently a mixture of the above glycoside picrate and sugar-free material. The third fraction did not yield a sparingly soluble picrate under the same conditions; it was finally obtained as a hygroscopic brownish resin. This resinous material was obviously impure, but it gave analytical values which suggested that it may have contained a considerable proportion of uncyclised 5-formamido-pyrimidine glycoside formed by a side-reaction from the thioformamido-compound.

The formulation of the above-mentioned picrate as that of 9-D-galactofuranosido-2-methylthioadenine rests upon its analysis, periodate titration, the similarity in ease of formation and solubility between it and the picrate of the 9-D-galactopyranoside, and the production of 9-glycosidopurines in analogous cases by the cyclisation procedure employed (cf. Kenner, Rodda, and Todd, *loc. cit.*). Owing to lack of material and the arduous nature of the synthetic route, a more extended examination of the final product has not been undertaken. The virtual certainty that it is correctly formulated as a 9-glycoside, however, justifies publication of our findings in their present form. Their main interest lies in the demonstration that synthesis of purine glycofuranosides by a route starting with acetylated furanose sugars is possible. The method is hardly likely to be of any practical value, partly because of low yields and partly because the sugar derivatives employed would normally be available only through the corresponding acetohalogenofuranoses. Under such conditions it would always be at a disadvantage as compared with either the modified Fischer method (Davoll, Lythgoe, and Todd, *J.*, 1948, 967) or the Schiff-base route (Kenner, Taylor, and Todd, *loc. cit.*) to purine glycofuranosides.

Experimental.

6-Amino-4-(tetra-acetyl D-galactopyranosidamino)-5-thioformamido-2-methylthiopyrimidine.—A solution of 6-amino-4-(tetra-acetyl D-galactopyranosidamino)-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine (2 g., Kenner, Lythgoe, and Todd, *loc. cit.*) in ethyl acetate (100 c.c.) was boiled under reflux in a nitrogen atmosphere with vigorous stirring. Zinc dust (12 g.) was added and then, dropwise during 15 minutes, a mixture of acetic acid (1·2 c.c.) and ethyl acetate (12 c.c.). The mixture was stirred and heated under reflux for 1 hour, and the resulting colourless solution filtered from zinc. The filter residue was washed with warm ethyl acetate, and the combined filtrate and washings were evaporated under reduced pressure in a stream of nitrogen. The residual resin was redissolved in a little ethyl acetate, and the 5-amino-glycoside precipitated as an amorphous powder (1·15 g.) by adding light petroleum (b. p. 40—60°).

The crude 5-amino-compound (2 g.) was dissolved in methanol (150 c.c.) at room temperature in a nitrogen atmosphere. A solution of sodium dithioformate (1·75 g.) in methanol (50 c.c.) was added, followed at once by acetic acid (0·53 g., 1 equiv.) in methanol (15 c.c.). Most of the liberated dithioformic acid remained in solution, and only a small amount of polymeric material separated. The mixture was left overnight, then boiled under reflux for 1 hour to precipitate the residual dithioformic acid, and filtered. The filtrate was evaporated under reduced pressure, and the residue dissolved in ethyl acetate and put on a column of neutral alumina. The column was washed with ethyl acetate and chloroform and then eluted with pyridine. The eluate was evaporated and the product recrystallised from ethanol. The *5-thioformamido-glycoside* formed small colourless needles, m. p. 145—148°, and had $[\alpha]_D^{15}$ +38° (±10°) (*c*, 1·10 in chloroform) (Found, in material dried at 100°/4 mm.: C, 43·8; H, 5·2; N, 12·6. $C_{20}H_{27}O_9N_5S_2$ requires C, 44·0; H, 5·0; N, 12·8%).

9-D-Galactopyranosido-2-methylthioadenine.—Sodium methoxide (65 mg.) was added to a solution of the above thioformamido-glycoside (260 mg.) in ethanol (20 c.c.) and the mixture was boiled under reflux in an atmosphere of nitrogen for 4 hours. The solution was treated with charcoal and allowed to cool, whereupon the *purine galactoside* separated as very small colourless crystals; concentration of the mother-liquors gave a further quantity of the same product (total yield, 50 mg.). Recrystallised from aqueous ethanol (50%), 9-D-galactopyranosido-2-methylthioadenine was obtained as colourless hydrated needles, m. p. 236—237°, which retained water of crystallisation tenaciously (Found, in material dried at 150°/4 mm. for 6 hours: C, 39·8; H, 5·5; N, 19·2. $C_{12}H_{17}O_5N_5S,H_2O$ requires C, 39·9; H, 5·3; N, 19·4%). The substance had $[\alpha]_D^{17}$ +25° (±10°) (*c*, 0·29 in water). Light absorption in ethanol: maximum, 2750 A. (ε = 15,500); minimum, 2500 A. (ε = 5450). Addition of picric acid to an ethanolic solution precipitated the *picrate* which dissolved in boiling water and separated again as a yellow powder which on heating decomposed at 280° (Found: C, 37·5; H, 3·6; N, 19·2. $C_{12}H_{17}O_5N_5S,C_6H_3O_7N_3$ requires C, 37·8; H, 3·5; N, 19·6%). On periodate titration the picrate absorbed 3·06 mols. of oxidant per mol.

6-Amino-4-(tetra-acetyl D-galactofuranosidamino)-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine.—Tetra-acetyl-D-galactofuranose (10 g.; Schlubach and Prochownik, *Ber.*, 1930, **63**, 2298) and 4 : 6-diamino-2-methylthiopyrimidine (15 g.) were heated under reflux in dry ethanol (200 c.c.) to which had been added concentrated sulphuric acid (0·3 g.) during 40 hours, water formed during the reaction being removed in the usual way by periodic addition of a benzene–ethanol mixture and slow distillation through a 20-cm. Fenske column fitted with a reflux-ratio head. Unchanged 4 : 6-diamino-2-methylthiopyrimidine separated on cooling and was collected by filtration. A further quantity of the same material was obtained by evaporating the filtrate under reduced pressure and extracting the residue with chloroform; most of the sugar-free pyrimidine remained undissolved (total recovery, 11 g.). The chloroform extract was evaporated and the residue dissolved in pyridine (70 c.c.). A neutral solution of diazotised 2 : 5-dichloroaniline (6·4 g.) was added and the mixture set aside for 3 hours before adding water (600 c.c.) and collecting the crude precipitated azo-derivative. The dried crude product was extracted with warm toluene, and the toluene solution allowed to cool, whereupon a quantity of sugar-free azo-compound separated. The mixture was filtered, the filtrate evaporated, and the residue dissolved in ethyl acetate and put on a column of neutral alumina (200 g.). Washing with ethyl acetate eluted the main broad red band from the column. The eluate was evaporated and the residue extracted with cold toluene which left a small amount of sugar-free material undissolved. The toluene solution was now chromatographed on neutral alumina (200 g.), the column being washed with toluene (1 l.). The broad red band which remained at the top of the column was pushed out and eluted with a mixture of pyridine and ethanol (1 : 1). Evaporation of the eluate gave an orange-red resin which was dissolved in toluene (25 c.c.), and light petroleum (b. p. 40—60°) was added gradually, giving a reddish-orange powder (2·83 g.) with an indefinite m. p. (115—140°) (Found, in material dried at 90°/0·1 mm.: N, 13·0. $C_{25}H_{32}O_9N_6Cl_2S$ requires N, 12·7%). Further purification was effected by dissolution in ether and careful reprecipitation with light petroleum, the *azo-furanoside* being obtained as an orange powder, m. p. 120—140° (Found, in material dried at 90°/0·1 mm.: C, 45·4; H, 3·9; N, 12·6. $C_{25}H_{32}O_9N_6Cl_2S$ requires C, 45·5; H, 4·3; N, 12·7%). The substance gave a positive Molisch test and had $[\alpha]_D^{16}$ +60° (±20°) (*c*, 0·095 in chloroform).

9-(Tetra-acetyl D-galactofuranosido)-2-methylthioadenine Picrate.—6-Amino-4-(tetra-acetyl D-galactofuranosidamino)-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine (1·1 g.) was reduced with zinc dust and acetic acid in ethyl acetate solution, and the product thioformylated exactly as described for the corresponding pyranose isomer (see above). The thioformamido-glycoside was obtained as a yellowish resin (0·43 g.) which could not be crystallised and was therefore use directly without further purification for the next stage in the synthesis.

The resinous thioformamido-glycoside (0·41 g.) was dissolved in dry acetonitrile (50 c.c.). Freshly fused potassium acetate (0·37 g.) was added and the solution stirred and heated under reflux for 10 hours, by which time evolution of hydrogen sulphide had practically ceased. The mixture was filtered and evaporated, and the residue taken up in chloroform and put on a column of neutral alumina (18 × 1·5 cm.). The column was washed with chloroform which slowly eluted the lowest narrow yellowish band;

evaporation of the eluate gave a resin *A* (110 mg.). Further elution with chloroform containing 5% ethanol (100 c.c.) gave a second resin *B* (140 mg.), which, although it contained carbohydrate material (positive Molisch reaction), did not form a picrate and was clearly not a purine glycoside. Resin *A* could not be crystallised; it was dissolved in ethanol (4 c.c.), boiled with charcoal, filtered, and cooled, and a saturated solution of picric acid in ethanol (1 c.c.) was added. There was immediate precipitation of a yellow *picrate* (39 mg.) which was purified by dissolution in ethyl acetate and reprecipitation with light petroleum (b. p. 40—60°). The product was apparently amorphous and melted rather indefinitely at *ca.* 120° (Found, in material dried at 75°/4 mm.: C, 43·2; H, 4·1; N, 15·0. $C_{20}H_{25}O_9N_5S,C_6H_3O_7N_3$ requires C, 42·2; H, 3·8; N, 15·1%).

9-D-*Galactofuranosido-2-methylthioadenine Picrate.*—The preparation of the crude acetylated 5-thioformamidofuranoside (0·5 g.) and its cyclisation by heating with potassium acetate in acetonitrile were carried out precisely as in the previous experiment. The crude cyclisation product was put on a column of neutral alumina as before and the column washed with chloroform (*ca.* 100 c.c.) which eluted a brownish resin *C* (160 mg.). Further washing with chloroform (200 c.c.) yielded a second resinous fraction *D* (180 mg.). A third Molisch-positive fraction *E* (240 mg.) was obtained by eluting the column with pyridine.

Resin *C* was dissolved in ethanol (charcoal), filtered, and cooled. Methanolic barium methoxide (0·8 c.c.; 0·155N.) was added to effect deacetylation. The deacetylated product separated out in part from the solution, but the main bulk (70 mg.) was obtained as a resin by neutralising the solution and evaporating to dryness. This residue gave a sparingly soluble picrate but, from analysis (Found: N, 18·1%) and periodate titration (8·6 mg. consumed 0·227 ml. of 0·268M-sodium metaperiodate), it was evidently not homogeneous; the resin consisted presumably of purine glycoside mixed with considerable amounts of other impurities.

Resin *D* was deacetylated in the same way as *A*, by methanolic barium methoxide (0·8 c.c.; 0·155N.). A small amount of amorphous material separated; this was filtered off, the filtrate evaporated, the residual resin which could not be crystallised dissolved in ethanol (4 c.c.), and saturated ethanolic picric acid (1 c.c.) added. The precipitated *picrate* (60 mg.) was collected after 24 hours. It could not be obtained in a crystalline state and was purified by precipitation from ethanolic solution with light petroleum (b. p. 40—60°). The product was an amorphous yellow powder, which softened somewhat at 170° and melted with decomposition at 250° (Found, in material dried at 90°/5 mm.: C, 38·1; H, 3·9; N, 19·2. $C_{13}H_{17}O_5N_5S,C_6H_3O_7N_3$ requires C, 37·8; H, 3·5; N, 19·6%).

Resin *E* was deacetylated in the same way as resins *C* and *D*, but the product did not give a sparingly soluble picrate. Attempted purification by fractional precipitation from ethanolic solution with light petroleum (b. p. 40—60°) gave a buff-coloured hygroscopic powder which rapidly changed to a brownish gum (Found, in material dried at 90°/5 mm.: C, 39·2; H, 5·8; N, 18·5. Calc. for $C_{13}H_{17}O_5N_5S,1\frac{1}{2}H_2O$: C, 38·9; H, 5·4; N, 18·9%). The fact that the analytical values obtained correspond to those calculated for the purine glycoside plus 1½ mols. of H_2O suggests that the material is not homogeneous and contains a considerable amount of uncyclised 5-formamido-compound.

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488. *Experiments on the Synthesis of Purine Nucleosides. Part XXV. 1 : 2 : 3 : 5-Tetra-acetyl* D-*Arabofuranose and the* D-*Arabofuranosides of Theophylline and Adenine.*

By N. W. BRISTOW and B. LYTHGOE.

The preparation of *5-trityl* D-*arabinose* and its conversion into 1 : 2 : 3 : 5-*tetra-acetyl* D-*arabofuranose* are described. The latter has been used to prepare acetobromo-D-arabofuranose from which D-*arabofuranosides* of *theophylline* and *adenine* have been synthesised; they belong to the α-series.

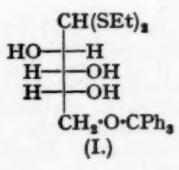
ALTHOUGH pyranosyl acetohalogeno-sugars have been widely used in synthetic work, only a limited use has been made of the furanosyl analogues. This is almost certainly due to the difficult accessibility of the latter; the fully acetylated *aldo*furanoses from which they can be prepared have been described only in two cases. In the hexose series, penta-acetyl D-galactofuranose has been obtained by acetylation of the parent hexose in hot pyridine solution (Schlubach and Prochownick, *Ber.*, 1929, **62**, 1502), and in the pentose series tetra-acetyl D-ribofuranose has been prepared indirectly from 5-trityl D-ribose (Howard, Lythgoe, and Todd, *J.*, 1947, 1052) and used in effecting syntheses of the natural nucleosides cytidine, adenosine, and guanosine (*loc. cit.*; Davoll, Lythgoe, and Todd, *J.*, 1948, 967, 1685). In the course of work with which we are at present engaged, including the synthesis of nucleoside analogues, the preparation of pentofuranose 1-phosphates, and investigations on the lactol ring structures of *o*-nitroaniline pentosides, we have felt the need for a general method whereby tetra-acetyl pentofuranoses could be obtained in quantity for use in the preparation of the corresponding acetohalogeno-sugars. Experiments designed to meet this need were therefore undertaken, and the present paper reports the results obtained by using D-arabinose as a representative pentose. Parallel investigations on D-xylose will be communicated later.

The method used by Howard, Lythgoe, and Todd for the preparation of tetra-acetyl D-ribofuranose cannot be applied in its entirety to pentoses such as arabinose and xylose, the stage lacking generality being that in which the pentose is converted into its 5-trityl derivative. In the case of ribose, this can be accomplished by direct interaction with trityl chloride in pyridine (Bredereck, Köthnig, and Berger, *Ber.*, 1940, **73**, 956), but when xylose or arabinose is treated in this way the desired product is not obtained, possibly owing to the smaller proportion of these sugars existing in the furanose form at equilibrium in solution; for instance, Zeile and Kruckenberg (*Ber.*, 1942, **75**, 1127) were able to isolate only small yields of a homogeneous product from the tritylation of xylose, and this proved to be a ditrityl derivative. For our purpose an indirect way of preparing 5-trityl pentoses was clearly necessary.

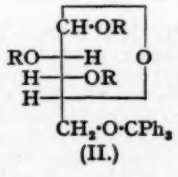
A suitable method seemed to lie in the removal of the alkylthio-groups from 5-trityl pentose mercaptals. *5-Trityl* D-*arabinose diethyl mercaptal* (I), obtained by tritylation of the parent mercaptal, does not appear to have been described, although the triacetate of the L-isomer was prepared by Wolfrom, Quinn, and Christman (*J. Amer. Chem. Soc.*, 1935, **57**, 713). Stirring with mercuric chloride and cadmium carbonate in aqueous acetone was not found satisfactory as a method for removing the ethylthio-groups from (I), since extensive detritylation took place simultaneously. No such difficulty was experienced when mercuric oxide was used in place of cadmium carbonate to neutralise the hydrochloric acid set free during the reaction, and *5-trityl* D-*arabinose* (II; R = H) was then isolated in good yield.

To convert (II; R = H) into tetra-acetyl D-arabofuranose the methods of Howard, Lythgoe, and Todd were used. The *triacetyl* derivative (II; R = Ac) could not be obtained crystalline, no doubt because both α- and β-forms were present. It was detritylated by hydrogenolysis in the presence of palladium, and after removal of triphenylmethane the product was acetylated to give 1 : 2 : 3 : 5-*tetra-acetyl* D-*arabinose* (III; R = OAc). Purified by vacuum distillation, the latter formed a clear, colourless syrup, from which no crystalline material could be obtained, even after chromatography on neutral aluminium oxide. Samples of the syrupy tetra-acetate obtained in different runs have been found to differ somewhat in optical rotation, and it seems clear that the product is a mixture of α- and β-forms in varying proportions, and that it is to this that its failure to crystallise is attributable. The high yields obtained when this material is used for the synthesis of the purine arabofuranosides described below, and the freedom of the products from contamination with the corresponding pyranosides, compounds which are much more readily isolable and much less readily soluble than the isomeric furanosides, provide evidence that the syrupy tetra-acetate is essentially homogeneous with respect to its lactol ring structure. Attention is directed to the high overall yield in which the tetra-acetate can be obtained (45% based on D-arabinose), which should make it a convenient starting material for the preparation of furanose derivatives.

When the crude acetobromo-compound (III; R = Br), obtained by treatment of (III; R = OAc) with liquid hydrogen bromide, was brought into reaction with theophylline silver in the usual manner, and the product deacetylated, a crystalline *theophylline-7-α-*D-*arabofuranoside* (IV) was obtained in good yield. The furanose structure of this compound was shown by oxidation with sodium metaperiodate, 1 mol. of which was consumed without



(I.)



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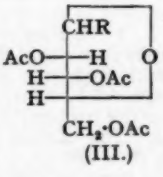
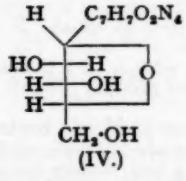
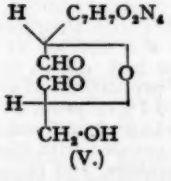


(III.)



(IV.)



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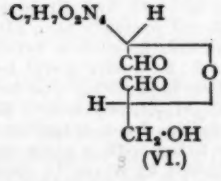

(VI.)

liberation of formic acid. The fission product formed in the oxidation must have the structure (V), since it differs markedly in solubility and molecular rotation from the dialdehyde (VI), which can be obtained as a crystalline substance by periodate oxidation of either theophylline-

7-β-D-glucopyranoside or theophylline-7-β-D-ribofuranoside (Lythgoe and Todd, *J.*, 1944, 595; Howard, Lythgoe, and Todd, *loc. cit.*). It follows that (IV) is an α-glycoside. The formation of an α-glycoside in this case is interesting, since it suggests that the acetobromo-compound from which it was formed may, like ordinary acetobromoarabopyranose, but unlike most acetobromo-sugars, be a β-form.

In order to obtain the arabofuranose isomer of adenosine, (III; R = Br) was condensed with 2 : 8-dichloroadenine silver, removal of the acetyl groups from the product then giving 2 : 8-*dichloro*-9-α-D-*arabofuranosidoadenine*. By reductive dehalogenation in the presence of a palladium catalyst this was transformed into 9-α-D-*arabofuranosidoadenine*, the furanose structure and configuration of which were established by periodate oxidation.

Unlike adenosine, the purine arabofuranosides described above contain a *trans*-α-glycol system as a feature of their sugar residues, and should therefore be capable of giving rise to 2′ : 3′-anhydro-compounds. The formation of such epoxides, and the possibilities of using them for the synthesis of deoxyglycosides and of other nucleoside derivatives, is now being studied and the results will be communicated later.

Experimental.

5-Trityl D-*Arabinose Diethyl Mercaptal* (I).—D-Arabinose diethyl mercaptal required for this experiment was prepared according to Fischer (*Ber.*, 1894, **27**, 677), but the reaction mixture was set aside overnight, then diluted with ice-water and set aside for a further 2 hours before the product was collected. In this way a 85% yield of material, m. p. 126°, was obtained. The solution obtained by allowing this material (58 g.) and trityl chloride (66·5 g.) to react in dry pyridine (350 c.c.) overnight was poured slowly into a well-stirred slurry of ice (800 g.) and water (600 c.c.). The precipitated syrup was dissolved in chloroform, the chloroform solution washed at 0° with sodium hydrogen sulphate solution, sodium hydrogen carbonate solution, and water, and finally dried and evaporated under reduced pressure. Crystallisation from benzene–light petroleum (b. p. 80—100°) gave *5-trityl* D-*arbinose diethyl mercaptal* as rosettes of prisms (103 g., 91%), m. p. 107°, $[\alpha]_D^{15}$ −37·5° (*c*, 3·1 in chloroform) (Found: C, 67·5; H, 6·8. $C_{28}H_{34}O_4S_2$ requires C, 67·5; H, 6·8%).

5-Trityl D-*Arabinose* (II; R = H).—The mercaptal (I) (99·5 g.), dissolved in aqueous acetone (900 c.c., containing 100 c.c. of water) in which yellow mercuric oxide (200 g.) was suspended, was stirred vigorously whilst a solution of mercuric chloride (225 g.) in acetone (700 c.c.) was allowed to run in slowly (2 hours). Stirring was continued for a further 15 hours, the solution filtered, evaporated under reduced pressure, and the residue extracted with chloroform (4 × 75 c.c.), a large quantity of mercuric chloride remaining undissolved. The chloroform extracts were washed with water, dried, and evaporated under reduced pressure. The residue was freed from chloroform by distillation with alcohol, and crystallised from a small volume of alcohol, giving *5-trityl* D-*arabinose* as fine needles (60 g., 76%), m. p. 68°, $[\alpha]_D^{15}$ +26·5° (6 minutes), +16·5° (25 hours (*c*, 2·0 in alcohol) (Found: C, 72·9; H, 6·8. $C_{24}H_{24}O_5$ requires C, 73·5; H, 6·1%). A crystalline form, m. p. 98°, was obtained by recrystallisation from mixtures of ethyl acetate, ether, and light petroleum (b. p. 40—60°); it had the same initial and final rotations as the form of m. p. 68°. The trityl compound is clearly of the α-series.

1 : 2 : 3-*Triacetyl* 5-*Trityl* D-*Arabinose* (II; R = Ac).—The above trityl compound (86 g.) in pyridine (150 c.c.) was added slowly to a well-stirred mixture of pyridine (150 c.c.) and acetic anhydride (250 c.c.) kept at −5°. After 3 days at room temperature, the solution was poured into ice and water (1 kg. each) with stirring, and the syrup separating was taken up in chloroform and washed and dried as usual. Removal of the solvent under reduced pressure gave the *triacetyl* compound as a gum, $[\alpha]_D^{15}$ 28·5° (*c*, 2·0 in chloroform) (Found: C, 69·7; H, 6·0. $C_{30}H_{30}O_8$ requires C, 69·5; H, 5·8%) (111 g., 98%). Variation of the acetylation conditions gave material whose optical rotation diverged by as much as 5° from that recorded above, which appears to reflect a difference in the proportions of α- and β-forms present in the syrup.

1 : 2 : 3 : 5-*Tetra-acetyl* D-*Arabinose* (III; R = OAc).—The preceding compound (111 g.), dissolved in anhydrous acetic acid (300 c.c.), was shaken at 40° in the presence of Adams's palladium oxide catalyst (1·8 g.) with hydrogen at atmospheric pressure. Absorption of 5·04 l. of hydrogen (theoretical = 5·18 l.) required 14 hours; the filtered solution was then evaporated under reduced pressure, and the majority of the triphenylmethane separated by crystallisation of the residue from the minimum quantity of alcohol. The mother-liquors were evaporated under reduced pressure, and extracted with light petroleum (3 × 200 c.c.; b. p. 40—60°) to remove any remaining triphenylmethane. The residue was dissolved in pyridine (200 c.c.), cooled to 0°, and treated with acetic anhydride (40 c.c.). After 24 hours the excess of acetic anhydride was destroyed by addition of alcohol, and the solution was concentrated under reduced pressure and, after dilution with chloroform, washed and dried as usual. Evaporation of the chloroform gave a syrup which was distilled at 130° (bath temp.)/10^{-3} mm. The colourless syrupy 1 : 2 : 3 : 5-*tetra-acetyl* D-*arabinose* had $[\alpha]_D^{15}$ in the range +16° to +29° (*c*, 2·5 in chloroform); the variation is probably due to varying proportions of α- and β-forms in the product (Found: C, 49·1; H, 5·8. $C_{13}H_{18}O_9$ requires C, 49·0; H, 5·7%); yield, 54 g. (79%).

Theophylline-7-α-D-*arabofuranoside*.—1 : 2 : 3 : 5-Tetra-acetyl D-arabinose (2·07 g.), contained in a steel tube fitted with a glass liner, was covered with liquid hydrogen bromide (15 c.c.), and the tube closed, allowed to warm to room temperature, and remain for a further ½ hour before being opened. After most of the excess of hydrogen bromide had been removed under reduced pressure, the last traces were removed by evaporating the product under reduced pressure with dry benzene. The crude acetobromo-compound was dissolved immediately in xylene (100 c.c.) containing dry finely divided theophylline silver (3·0 g.), and the mixture heated under reflux for ½ hour, then filtered, cooled, and

treated with a large volume of light petroleum (b. p. 40—60°). The precipitate was collected, dissolved in hot benzene (30 c.c.), and set aside at room temperature for 48 hours. The small quantity of theophylline which separated was filtered off, the solution evaporated under reduced pressure, and the residue dissolved in 0·155N-methanolic barium methoxide (30 c.c.). After 24 hours at room temperature, barium was removed by addition of sulphuric acid and the solution filtered and evaporated. Crystallisation of the residue from alcohol gave *theophylline*-7-α-D-*arabofuranoside* (1·3 g., 62%), m. p. 173°, $[\alpha]_D^{15}$ +21° (*c*, 1·3 in water) (Found: C, 46·2; H, 5·3; N, 17·8. $C_{12}H_{16}O_6N_4$ requires C, 46·2; H, 5·1; N, 18·0%). The compound is very soluble in water.

Periodate oxidation. Sodium metaperiodate consumed: 1·06 mols. per mol. of glycoside. Formic acid liberated: nil. Rotation of fission product, determined from the solution on completion of the oxidation: $[M]_D^{16}$ −0·78 × 10⁴. Lythgoe and Todd (*loc. cit.*) give for the fission product from theophylline-7-β-D-glucopyranoside $[M]_D^{15}$ −1·29 × 10⁴.

2 : 8-*Dichloro*-9-α-D-*arabofuranosidoadenine*.—Crude acetobromo-D-arabofuranose (prepared as described above, from 4·5 g. of 1 : 2 : 3 : 5-tetra-acetyl D-arabinose) was dissolved in dry xylene (100 c.c.) containing dry, finely divided 2 : 8-dichloroadenine silver (4·1 g.), and the suspension heated under reflux for 3 hours and then filtered. To the cooled filtrate light petroleum (350 c.c., b. p. 60—80°) was added, and the precipitate collected, dried, and recrystallised from alcohol. The product was set aside for 12 hours at 0° with methanol (50 c.c.) and methanolic ammonia (65 c.c., saturated at 0°), the solution evaporated under reduced pressure, and the residue crystallised from hot water (charcoal). The 2 : 8-*dichloro*-9-α-D-*arabofuranosidoadenine* separated as needle tufts (1·35 g., 28%), m. p. 222° (decomp.; rapid heating) (Found: C, 35·6; H, 3·1; N, 20·1. $C_{10}H_{11}O_4N_5Cl_2$ requires C, 35·7; H, 3·3; H, 20·8%).

9-α-D-*Arabofuranosidoadenine*.—A solution of the above dichloro-compound in water (200 c.c.) to which N-sodium hydroxide (7 c.c.) and a 5% palladium–barium sulphate catalyst (1 g.) had been added was shaken with hydrogen at room temperature for 3 hours, after which no more hydrogen was absorbed. The solution was filtered, neutralised with hydrochloric acid, and concentrated to 7 c.c. under reduced pressure. The 9-α-D-*arabofuranosidoadenine* was collected and recrystallised from hot water; it formed small rosettes of needles (0·69 g., 75%), m. p. 208°, $[\alpha]_D^{17}$ +69° (*c*, 1·1 in water) (Found: C, 44·8; H, 4·6; N, 25·8. $C_{10}H_{13}O_4N_5$ requires C, 44·9; H, 4·9; N, 26·2%). A further quantity of the same material was isolated as the *picrate* by addition of picric acid to the mother-liquors; this showed no m. p. below 360° (Found: C, 38·7; H, 3·2; N, 22·9. $C_{10}H_{13}O_4N_5,C_6H_3O_7N_3$ requires C, 38·7; H, 3·2; N, 22·6%).

Periodate oxidation. 9-α-D-Arabofuranosidoadenine consumed 0·97 mol. of sodium metaperiodate per mol., and liberated no formic acid. Treatment of the solution with picric acid when the oxidation was complete gave the *picrate*, $[M]_D^{14}$ 0·4 × 10⁴ (*c*, 0·3 in 0·1N-sodium hydrogen carbonate) (Found: C, 39·3; H, 3·0; N, 22·0. $C_{10}H_{11}O_4N_5,C_6H_3O_7N_3$ requires C, 38·9; H, 2·9; N, 22·7%), of the fission product. Davoll, Lythgoe, and Todd (*J.*, 1946, 833) give for the similar picrate from adenosine $[M]_D^{14}$ −1·08 × 10⁴ (*c*, 1·2 in 0·1N-sodium hydrogen carbonate). This difference shows that 9-α-D-arabofuranosidoadenine belongs to the α-series.

Grateful acknowledgment is made to Professor A. R. Todd, F.R.S., for his interest in this work and to the Department of Scientific and Industrial Research for a Maintenance Grant (to N. W. B.).

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489. *Experiments on the Interaction of Hydroxy-compounds and Phosphorus and Thionyl Halides in the Absence and in the Presence of Tertiary Bases. Part VI.*

By MARIANNE C. BERLAK and WILLIAM GERRARD.

To elucidate further the mechanism of replacement of a hydroxyl group by halogen, we have examined the reaction of phosphorus tri-iodide with various alcohols in carbon disulphide solution. The experiments were conducted at temperatures below 15—20°, no attempt being made to force subsequent reactions on the system. Yields of iodide were determined for different molecular proportions of reagents and for different reaction times. (+)-Butan-2-ol and (+)-octan-2-ol afforded the respective (−)-iodides, with inversion and little or no loss in rotatory power, and an interesting effect of branching is revealed by low yields of *iso*propyl and *iso*butyl iodide.

Addition of the tri-iodide (0·34 mol.) to the alcohol (1 mol.) and pyridine (1 mol.) gave pyridine hydriodide and no alkyl iodide, but the latter product was formed on further addition of tri-iodide. Evidence that dialkyl hydrogen phosphites, $(RO)_2P{\cdot}OH$, interact much more readily with hydrogen iodide than with hydrogen chloride or hydrogen bromide is provided.

IN the table are recorded the yields of iodide resulting from the interaction of alcohols and phosphorus tri-iodide dissolved in carbon disulphide. The influence of a change in molecular proportions of the reagents, and the influence of the time for which the reagents were allowed to remain in contact were in some measure studied. Temperatures, however, were in the main kept below 15—20°, and no attempt was made to force subsequent reactions on the system by the use of higher temperatures. The solvent was used in order to avoid heterogeneity and thus to ensure a more reliable basis for comparison with the phosphorus trichloride– and phosphorus tribromide–alcohol systems (Gerrard, *J.*, 1944, 85; 1945, 848).

Alcohol, 1 mol.	PI_3, mols.	Time, hours.	Yield of RI, %.	B. p.	I, %, in RI. Found.	I, %, in RI. Calc.	Weight of residue containing phosphorus, as wt.-% of alcohol.
1. Pr^nOH	0·33	24	40	100—102°	74·1	74·7	10
2. Pr^iOH	0·33	24	20	85— 89	—	—	9
	0·33	72	21	87— 88	74·3	74·7	—
	1·0	24	18	87— 89	74·1	74·7	—
3. Bu^nOH	0·33	24	43	126—128	68·0	69·0	20
	0·33	72	61	126—129	68·0	—	9
	0·33	2·5 (b. p.)	48	127—129	68·5	—	2
	1·0	24	56	127—128	68·4	—	4
	1·0	72	56	128—129	68·5	—	—
4. Bu^sOH	*a* 0·33	24	60	115—118	67·9	69·0	12
	0·33	72	58	117—118	68·2	—	—
	c 1·0	24	61	116—117	68·2	—	—
5. Bu^iOH	*a* 0·33	24	20	112—115	67·8	69·0	—
	b 0·33	74	20	115—116	69·0	—	—
	c 1·0	24	17	115—117	68·0	—	—
6. $Bu^s{\cdot}CH_2{\cdot}OH$	*a* 0·33	24	48	140—143	60·1	64·1	—
	b 0·33	68	44	142—143	63·2	—	—
	1·0	24	45	143—144	63·0	—	15
7. $CHPr^n_2{\cdot}OH$	0·33	24	74	81°/21 mm.	55·5	56·1	—
	1·0	24	80	77— 78°/20 mm.	55·7	—	—
8. $n\text{-}C_6H_{17}{\cdot}OH$	0·33	24	42	103—105°/15 mm.	50·9	52·9	—
	1·0	24	56	108°/18 mm.	52·8	—	—
9. $n\text{-}C_6H_{13}{\cdot}CHMe{\cdot}OH$	*a* 0·33	24	36	90— 92°/16 mm.	41·8	52·9	—
	b 0·66	24	66	89— 90°/15 mm.	50·0	—	—
	c 0·66	72	66	87— 88°/14 mm.	50·0	—	—
	d 1·0	24	75	90°/15 mm.	52·6	—	—

4 (*a*) RI, a_D^{21} +21·0°; from ROH, a_D^{21} −4·3°. (*c*) RI, a_D^{22} +20·6°; from ROH, a_D^{21} −4·3°.

5 (*a*) Also distillate (20%), b. p. 133—140°/24 mm. [Found: I, 5·7; P, 14·0. Calc. for $(RO)_3PHO$: P, 16·0%]. (*b*) Also distillate (50%), b. p. 124—126°/15 mm. (Found: P, 13·9%). (*c*) Also distillate (30%), b. p. 126—128°/22 mm. (Found: I, 2·4; P, 15·6%).

6 (*a*) Also distillate (12%), b. p. 160°/17 mm. (decomp.) [Found: P, 11·8. Calc. for $(RO)_2PHO$: P, 13·9%]. (*b*) Residue (10%) (Found: P, 12·5%).

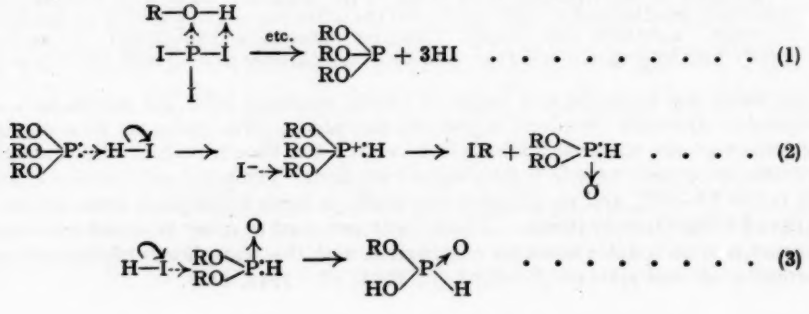
9 (*a*) RI + ROH, a_D^{16} −39·0°; from ROH, a_D^{16} +7·8°. Almost identical results were obtained after 48 and 72 hours. (*b*) RI, a_D^{16} −57·4°; from ROH, a_D^{16} +7·8°. (*c*) RI, a_D^{16} −57·0°; from ROH, a_D^{16} +7·8°. (*d*) RI, a_D^{16} −59·5°; from ROH, a_D^{16} +7·8°.

(In all rotations, $l = 1$ dm.)

An increase in the molecular proportion of the tri-iodide from 0·33 to 1·0 mol., or in the time (from 24 to 72 hours) during which the reagents were in contact, did not markedly increase the yield in most of examples studied. From this it appears that the iodide is formed during the early part of the first 24-hour period, and a fine-scale study of this system is now being made.

An interesting feature is the low yield of *iso*propyl and *iso*butyl iodide. These are probably produced by a comparatively quick reaction which stops when the material concerned in the final attachment of the iodine atom has been exhausted, whereas in the other examples a second reaction can proceed beyond the first.

By analogy with the trichloride and tribromide systems (Gerrard, *loc. cit.*) it may be supposed that the phosphite, $(RO)_3P$, is built up by successive broadside, four-centre approaches (1), but is rapidly attacked by hydrogen iodide, the latter reaction involving the lone pair of electrons on the phosphorus atom (2):



We believe that the dialkyl hydrogen phosphite, $(RO)_2PHO$, is available for further interaction with hydrogen iodide by a mechanism (3), which is not only different but proceeds much less readily. With hydrogen bromide, the mechanism (3) proceeds even less readily, and with hydrogen chloride still less so. It might be in the reluctance to replacement of the second alkyl group (reaction 3) that propan-2-ol and 2-methylpropan-2-ol differ from the other alcohols examined.

That the final attachment of the iodine atom is by an end-on approach (as in 2 and 3) is evident from the fact that (−)-2-iodobutane and (−)-2-iodo-octane were obtained from the respective (+)-alcohols with little or no loss in rotatory power, and the signs of rotation show that the iodides were produced by inversion (cf. Kenyon and Phillips, *Trans. Faraday Soc.*, 1930, **26**, 451; Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1196, 1201, 1208, 1243, 1252).

It will be seen that phosphorus tri-iodide can function instead of hydrogen iodide according to mechanism (3), because the hydrogen phosphite prepared from (−)-octan-2-ol interacted with the tri-iodide at room temperature to yield (+)-2-iodo-octane, α_D^{24} +62·6° (l = 1 dm.), in 69% yield, this value probably representing full activity.

The influence of pyridine in the tri-iodide system is essentially the same as in the trichloride and tribromide systems, in that the broad-side approach (1) is greatly facilitated and halogen is precipitated as pyridine hydrohalide. The tri-iodide behaved differently in so far as it produced alkyl halide when it was added to the reaction mixture in amounts greater than 0·33 mol. for each mol. of alcohol and base.

Experimental.

(For all rotations, l = 1 dm., unless otherwise stated.)

Interaction of Phosphorus Tri-iodide and Alcohols in Carbon Disulphide Solution.—A solution of phosphorus tri-iodide (280 g. per l.) was prepared by the addition of the calculated amount of white phosphorus to a solution of iodine in carbon disulphide. Calculated amounts of this solution and of the alcohol were mixed at −10°, and the resulting solution was allowed to stand at room temperature for the time stated, after which it was washed with water and then dilute aqueous sodium carbonate, and finally dried (Na_2SO_4). Carbon disulphide was removed and the product was distilled. Results are recorded in the table.

Interaction of Phosphorus Tri-iodide and Alcohols in the Presence of Pyridine.—(+)-Octan-2-ol (6·5 g., 1 mol.; α_D^{16} +7·8°) and pyridine (3·95 g., 1 mol.) in carbon disulphide (50 c.c.) were cooled to −10°. A precipitate formed during the dropwise addition of a solution of phosphorus tri-iodide (6·9 g., 0·33 mol.) in carbon disulphide. After 4 hours at 15°, the precipitate (9·3 g. Calc. for C_5H_5N,HI: 10·3 g.) was separated, and to the filtrate at −10° phosphorus tri-iodide (13·8 g., 0·66 mol.; in carbon disulphide) was added. After 66 hours at 15°, the mixture was washed as described above. (−)-2-Iodo-octane (7·78 g.), b. p. 98—100°/18 mm., α_D^{18} −56·8° (Found: I, 51·0%), was obtained. There was no residue.

Butan-1-ol (7·4 g., 1 mol.), pyridine (7·9 g., 1 mol.), and carbon disulphide (50 c.c.) were mixed and cooled to −10°. Dropwise addition of phosphorus tri-iodide (13·7 g., 0·33 g.) in the same solvent caused a steady precipitation of pyridine hydriodide (17·9 g. Calc.: 20·7 g.) (Found: I, 60·0; C_5H_5N, 38·0. Calc.: I, 61·2; C_5H_5N, 38·3%). After being at 15° for 2 hours, the mixture was filtered, and the filtrate was washed and dried as usual. The residue (6·8 g.) remaining when the solvent was evaporated afforded a distillate, b. p. 145—150°/20 mm. [Found: P, 13·3. Calc. for $(RO)_3P$: P, 12·4%], but there was much decomposition.

The tri-iodide (20·6 g., 0·33 mol.; in carbon disulphide) was added to a solution of butan-1-ol (11·1 g., 1 mol.) and pyridine (11·83 g., 1 mol.) in carbon disulphide (100 c.c.) as before. Without filtration, a further quantity of tri-iodide (0·66 mol.) was added, and the mixture was set aside for 66 hours at 15°. From the washed and dried organic solution, *n*-butyl iodide (6·9 g.), b. p. 126—127° (Found: I, 68·4%), and 3·90 g. of undistillable residue [Found: I, 0; P, 15·7. Calc. for $(RO)_2POH$: P, 16·0%] were obtained.

Octan-1-ol (13 g., 1 mol.), pyridine (1 mol.), and phosphorus tri-iodide (0·33 mol.), by the same prodedure, afforded pyridine hydriodide (85%) (Found: I, 60·7; C_5H_5N, 37·0%), and by the further addition of tri-iodide (0·66 mol.) *n*-octyl iodide (14·1 g.), b. p. 103—104°/15 mm. (Found: I, 52·9. Calc. for $C_8H_{17}I$: I, 52·9%), and 1·2 g. of residue were obtained.

Interaction of Phosphorous Esters and Hydrogen Iodide.—Through (−)-dimethylhexylcarbinyl hydrogen phosphite (4·6 g.; α_D^{22} −12·6°), cooled at −10°, dry hydrogen iodide was passed for 1 hour, although absorption appeared to cease after 45 minutes. After 18 hours at 15°, the mixture was treated with ice and a dilute solution of sodium carbonate, and extracted with ether. From the dried ethereal extract, (+)-2-iodo-octane (5·93 g.), b. p. 101—102/23 mm., α_D^{20} +45·8° (Found: I, 51·9%), and 0·4 g. of residue were obtained.

Hydrogen iodide was passed into di-*n*-butyl hydrogen phosphite (6·5 g.) at −10° for 50 minutes, absorption appearing complete after 30 minutes. After a further 30 minutes at −10°, the mixture was treated with ice and a dilute solution of sodium carbonate as previously described. *n*-Butyl iodide (2·65 g.), b. p. 127—130° (Found: I, 68·0%), and the hydrogen phosphite (2·03 g.), b. p. 130—131°/23 mm. [Found: P, 16·1. Calc. for $(RO)_2PHO$: P, 16·0%], were obtained from the ethereal solution. The sodium carbonate extract, on acidification with dilute sulphuric acid, afforded the dihydrogen phosphite (1·2 g.) [Found: P, 21·0. Calc. for $C_4H_9O{\cdot}P(OH)_2$: P, 22·5%] as an undistilled residue.

When the hydrogen iodide was passed into di-*n*-butyl hydrogen phosphite without external cooling, the temperature rose from 19° to 23°, absorption appearing complete after 30 minutes. Although the temperature was raised to 40°, no more absorption occurred. By the procedure described above,

n-butyl iodide (5·3 g.), b. p. 127—130° (Found: I, 68·2%), 0·26 g. of residue, and, from the sodium carbonate extract, the dihydrogen phosphite (1·5 g.) (Found: P, 21·9) were obtained.

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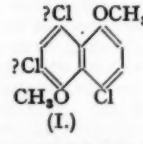
490. *The Stereochemistry of Some Aromatic Ethers.*

By K. B. EVERARD and L. E. SUTTON.

The electric dipole moments of 1 : 5- and 1 : 4-dimethoxynaphthalene are shown to be 0·67 and 2·09 D., respectively. The difference between these and that of the analogous quinol dimethyl ether (1·73 D.) is believed to be due to (i) the fixation of the methoxy-groups in the plane of the rings by resonance involving the use of a π-orbital between these groups and the rings, and (ii) the steric inhibition by the *peri*-hydrogen atoms of one of the two coplanar configurations which each methoxy-group can assume.

The moments of 4 : 8-dichloro- and -dibromo-1 : 5-dimethoxynaphthalene are found to be 0·95 and 0·93 D., *i.e.*, greater than that of the parent ether. It is suggested that the *peri*-substituents force one another out of the plane of the rings, giving rise to three different configurations, two of which are not centrosymmetrical (and hence may possess a dipole moment): these two configurations should be optically antimeric. The application of this hypothesis to explain some other anomalous moments is explored.

By chlorinating 1 : 5-dimethoxynaphthalene, Thomson (*J. Org. Chem.*, 1948, **13**, 371) obtained the compound 4 : *x*-dichloro-1 : 5-dimethoxynaphthalene (I) in which he believed *x* to be either 6 or 8. He suggested that, in order to settle this orientation, the electric dipole moment of this compound should be compared with that of 1 : 5-dimethoxynaphthalene. If *x* were 8 the two moments should be the same, by symmetry, whereas the isomer should be distinguishable by a higher moment (*ca.* 2·6 D.).



(I.)

The dipole moments of the two compounds were measured in benzene solution at 25°. The values obtained threw unexpected light on the stereochemistry of naphthalene derivatives, and suggested that the measurement of additional compounds would provide fruitful results. Those which have been examined are: 1 : 4-dimethoxynaphthalene, 4 : 8-dibromo-1 : 5-dimethoxynaphthalene, quinol dimethyl ether, anisole, 1-methoxynaphthalene, and 2 : 5-dichloroquinol dimethyl ether.

EXPERIMENTAL.

(Temperatures are uncorrected.)

Preparation and Purification of Materials.—"AnalaR" Benzene was purified by freezing out thrice, drying (P_2O_5), and distilling it over phosphoric oxide in a stream of dry air under which it was stored until required.

Samples of 1 : 4- and 1 : 5-dimethoxynaphthalene and the dichloro- and dibromo-derivatives of the latter were supplied by Dr. R. H. Thomson. Their m. p.s were given respectively as 88°, 181°, 159°, and 189°. In every case the m. p. range was less than 1°.

Quinol dimethyl ether was prepared by Vermeulen's method (*Rec. Trav. chim.*, 1906, **25**, 28), thrice recrystallised from aqueous ethanol, and finally sublimed in a vacuum; m. p. 55·6—56·0° (Vermeulen gives 55—56°).

A specimen of anisole was kindly provided by Mr. J. W. Bayles, who had purified it by successive treatment with potassium hydroxide and phosphoric oxide, followed by two distillations at 152·5—153°. It was distilled a third time before use; b. p. 153°.

1-Methoxynaphthalene was prepared by Gattermann's method (*Annalen*, 1888, **244**, 72). It was distilled twice under atmospheric pressure [b. p. 265—265·5°: 269°/753·1 mm. (corr.), Nasini and Bernheimer, *Gazzetta*, 1885, **15**, 79; 265—266°, Marchetti, *ibid.*, 1879, **9**, 545; 258°, Staedel, *Annalen*, 1883, **217**, 42] and once under reduced pressure, at 133°/11 mm. (Found: C, 83·80; H, 6·37. Calc. for $C_{11}H_{10}O$: C, 83·6; H, 6·3%).

2 : 5-Dichloroquinol dimethyl ether was made by methylating the quinol. The latter, which had been made by Hammick, Hampson, and Jenkins (*J.*, 1938, 1263), was purified by recrystallisation from water and benzene and sublimation in a vacuum (m. p. 167—168°). 7 G. of this were heated under reflux with 7 ml. of methyl sulphate and 16 ml. of 5N-sodium hydroxide for 5 minutes. The brown solid which formed on cooling was triturated with 2N-sodium hydroxide to remove phenolic material, twice recrystallised from ethanol, and sublimed in a vacuum. The 3·4 g. of pure white crystals thereby obtained melted at 131—131·5° (126° Habermann, *Ber.*, 1878, **11**, 1034; Ciamician and Silber, *Gazzetta*, 1892, **22**, 59, give 131° for x,x-dichloroquinol dimethyl ether; constitution proved by Kohn and Gurewitsch, *Sitz. Akad. Wiss. Wien*, 1939, **139**, 405).

Physical Measurements.—Electric dipole moments were computed from measurements of dielectric constant, specific volume, and refractive index of benzene solutions by the procedure described by

Halverstadt and Kumler (*J. Amer. Chem. Soc.*, 1942, **64**, 2988), in which ε_1, v_1, and n_1 are obtained by extrapolation to $\omega_2 = 0$. The symbols have the same significance as in Halverstadt and Kumler's paper.

Dielectric constants were measured at 25° with a heterodyne capacity meter designed by R. A. W. Hill and L. E. Sutton (description to be published) in conjunction with a condenser similar to that described by Jenkins and Sutton (*J.*, 1935, 609).

Specific volumes were measured at 25° with a 10-ml. Sprengel–Ostwald pyknometer.

Refractive indices relative to that of benzene were measured with a Jamin interferometer of Kuhn and Wheatley's design (*J. Sci. Instr.*, 1945, **22**, 110). It was later found, however, that the error associated with such instruments (Weissberger, " Physical Methods of Organic Chemistry," Interscience, 1945, p. 728) when the substances examined have large dispersions, was giving spurious values in all cases other than anisole and quinol dimethyl ether. Accordingly, all the dimethoxynaphthalenes and 2 : 5-dichloroquinol dimethyl ether were re-examined with a Pulfrich refractometer, and the values reported are those so obtained for them. The molar refraction of 1-methoxynaphthalene was calculated from Nasini and Bernheimer's data (*loc. cit.*).

The dielectric constant of pure dry benzene used to calibrate the condenser was taken as 2·2727 at 25° (Hartshorn and Oliver, *Proc. Roy. Soc.*, 1929, **123**, *A*, 664), and its refractive index as 1·50144 (20°, for interferometer) or 1·49794 (25°, Pulfrich refractometer).

All dipole moments are given in Debye units.

Refractive Index Data.

Compound.	ω_2.	Δn_D^{25}.
1 : 4-Dimethoxynaphthalene	0·01410	0·00127
1 : 5-Dimethoxynaphthalene	0·01251	0·00123
4 : (8)-Dichloro-1 : 5-dimethoxynaphthalene	0·03551	0·00373
4 : 8-Dibromo-1 : 5-dimethoxynaphthalene	0·01905	0·00183
2 : 5-Dichloroquinol dimethyl ether	0·01740	0·00079

1 : 4-*Dimethoxynaphthalene.*

ω_2.	ε_{12}.	v_{12}.	Δn.	ω_2.	ε_{12}.	v_{12}.	Δn.
0·002202	2·2792	1·1445	—	0·010206	2·3014	1·1422	—
0·004793	2·2865	1·1439	—	0·012484	2·3079	1·1417	—
0·008085	2·2955	1·1430	—				

$\varepsilon_{12} = 2{\cdot}2731 + 2{\cdot}782\,\omega_2$; $v_{12} = 1{\cdot}1452 - 0{\cdot}283\,\omega_2$; ${}_TP_2 = 146{\cdot}8$ c.c.;
${}_EP_2 = 57{\cdot}2$ c.c.; $\mu = 2{\cdot}09 \pm 0{\cdot}02$.

1 : 5-*Dimethoxynaphthalene.*

0·003913	2·2745	1·1441	—	0·008666	2·2767	1·1426	—
0·005801	2·2757	1·1433	—	0·011158	2·2785	1·1422	—

$\varepsilon_{12} = 2{\cdot}2724 + 0{\cdot}534\,\omega_2$; $v_{12} = 1{\cdot}1450 - 0{\cdot}253\,\omega_2$; ${}_TP_2 = 68{\cdot}9$ c.c.;
${}_EP_2 = 59{\cdot}8$ c.c.; $\mu = 0{\cdot}67 \pm 0{\cdot}1$.

This supersedes the result quoted by Thomson (*loc. cit.*).

4 : (8)-*Dichloro*-1 : 5-*dimethoxynaphthalene.*

0·004957	2·2766	1·1433	—	0·014769	2·2833	1·1387	—
0·009104	2·2795	1·1413	—	0·019221	2·2864	1·1369	—

$\varepsilon_{12} = 2{\cdot}2732 + 0{\cdot}683\,\omega_2$; $v_{12} = 1{\cdot}1455 - 0{\cdot}451\,\omega_2$; ${}_TP_2 = 86{\cdot}2$ c.c.;
${}_EP_2 = 67{\cdot}8$ c.c.; $\mu = 0{\cdot}95 \pm 0{\cdot}05$.

This supersedes the result quoted by Thomson (*loc. cit.*).

4 : 8-*Dibromo*-1 : 5-*dimethoxynaphthalene.*

0·004573	2·2758	1·1425	—	0·011087	2·2789	1·1385	—
0·007547	2·2775	1·1408	—	0·014162	2·2813	1·1367	—

$\varepsilon_{12} = 2{\cdot}2732 + 0{\cdot}553\,\omega_2$; $v_{12} = 1{\cdot}1453 - 0{\cdot}609\,\omega_2$; ${}_TP_2 = 91{\cdot}3$ c.c.;
${}_EP_2 = 73{\cdot}4$ c.c.; $\mu = 0{\cdot}93 \pm 0{\cdot}03$.

Quinol dimethyl ether.

0·005524	2·2862	1·1435	0·00011	0·016135	2·3113	1·1415	0·00038
0·010234	2·2971	1·1427	0·00022	0·020366	2·3221	1·1403	0·00047
0·013667	2·3055	1·1419	0·00031				

$\varepsilon_{12} = 2{\cdot}2725 + 2{\cdot}418\,\omega_2$; $v_{12} = 1{\cdot}1447 - 0{\cdot}211\,\omega_2$; $\Delta n = -0{\cdot}00003 + 0{\cdot}025\,\omega_2$;
${}_TP_2 = 101{\cdot}3$ c.c.; ${}_EP_2 = 40{\cdot}0$ c.c.; $\mu = 1{\cdot}73 \pm 0{\cdot}01$.

Other values: 1·67, 1·81, 1·73 (*Trans. Faraday Soc.*, 1934, **30**, Appendix), 1·70 (Mizushima, Morino, and Okazaki, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1938, **34**, 1147), and 1·73 (Meyer, *Z. physikal. Chem.*, 1930, *B*, **8**, 27).

Anisole.

ω_2.	ε_{12}.	v_{12}.	Δn.	ω_2.	ε_{12}.	v_{12}.	Δn.
0·002441	2·2769	1·1444	0·00006	0·014959	2·2976	1·1429	0·00026
0·006311	2·2833	1·1441	0·00012	0·019498	2·3056	1·1421	0·00036

$\varepsilon_{12} = 2{\cdot}2727 + 1{\cdot}684\,\omega_2$; $v_{12} = 1{\cdot}1449 - 0{\cdot}136\,\omega_2$; $\Delta n = 0{\cdot}00001 + 0{\cdot}018\,\omega_2$;
${}_TP_2 = 66{\cdot}8$ c.c.; ${}_EP_2 = 33{\cdot}3$ c.c.; $\mu = 1{\cdot}28 \pm 0{\cdot}01$.

Other values : 0·8 (Estermann, *Z. physikal. Chem.*, 1928, *B*, **1**, 134), 1·16, 1·23 (*Trans. Faraday Soc.*, 1934, **30**, Appendix), 1·22 (Phadke, Gokhale, Phalnikar, and Bhide, *J. Indian Chem. Soc.*, 1945, **22**, 235), 1·35 (Groves and Sugden, *J.*, 1937, 1782), and 1·54 (Böttcher, *Physica*, 1939, **6**, 59).

1-*Methoxynaphthalene.*

0·004638	2·2789	1·1439	—	0·015188	2·2936	1·1415	—
0·005636	2·2809	1·1434	—	0·017329	2·2969	—	—
0·014990	2·2934	1·1413	—				

$\varepsilon_{12} = 2{\cdot}2727 + 1{\cdot}381\,w_2$; $v_{12} = 1{\cdot}1448 - 0{\cdot}228\,w_2$; ${}_TP_2 = 84{\cdot}3$ c.c.;
${}_EP_2 = 50{\cdot}9$ c.c.; $\mu = 1{\cdot}28 \pm 0{\cdot}03$.

2 : 5-*Dichloroquinol dimethyl ether.*

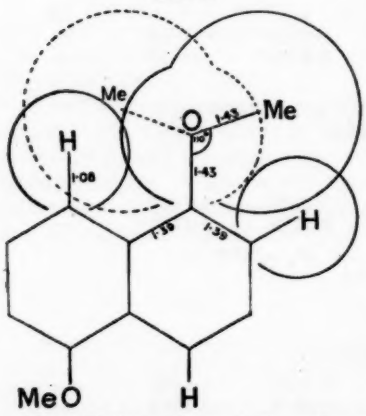
0·002634	2·2740	1·1440	—	0·008367	2·2779	1·1416	—
0·005489	2·2759	1·1427	—	0·010525	2·2793	1·1406	—

$\varepsilon_{12} = 2{\cdot}2723 + 0{\cdot}675\,\omega_2$; $v_{12} = 1{\cdot}1451 - 0{\cdot}420\,\omega_2$; ${}_TP_2 = 71{\cdot}0$ c.c.;
${}_EP_2 = 49{\cdot}4$ c.c.; $\mu = 1{\cdot}03 \pm 0{\cdot}02$.

Discussion.

The dipole moment of 1 : 5-dimethoxynaphthalene is 0·67 : therefore if $x = 8$ the moment of 4 : x-dichloro-1 : 5-dimethoxynaphthalene should likewise be 0·67, since that of 1 : 5-dichloronaphthalene is zero (this and other dipole moments are taken from *Trans. Faraday Soc.*, 1934, **30**, Appendix). If, however, $x = 6$, then the moment of the compound should approximate to that of 1 : 7-dichloronaphthalene, *viz.*, 2·6. Other values of x would give, on the same basis, moments of 1·85 ($x = 2$), 2·4 (3), and 1·4 (7), but these are ruled out on organic chemical grounds (Thomson, *loc. cit.*). The measured value of the moment of the dichloro-compound is 0·95. The melting point shows the substance to be pure, and not a mixture. The moment therefore shows beyond reasonable doubt that the first-mentioned alternative ($x = 8$) is correct.

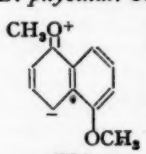
Fig. 1.



The full lines represent the methoxy-group in the cis*-position ; the dotted lines, in the* trans*-position. This and other scale diagrams are based on dimensions given in Pauling's " Nature of the Chemical Bond."*

There is, however, not only a considerable and unexpected discrepancy between the moments of the parent substance and its dichloro-derivative, but the absolute magnitudes of both occasion some surprise, in that they are not equal to that of the benzene analogue, quinol dimethyl ether (1·73). This last moment is usually regarded as arising from the free rotation of the methoxy-groups about the C_{aryl}–O bonds, giving all configurations from *cis* to *trans* with equal probability (though an equal mixture of these extreme configurations would possess the same dipole moment). It seems that in 1 : 5-dimethoxynaphthalene free rotation is much reduced and that the methoxy-groups are constrained to lie approximately *trans* to each other.

The steric effect of the hydrogen atoms situated *peri* to the substituents is sufficient only to prevent each methoxy-group from swinging to within about 60° of one of the coplanar positions; and it may be shown by integrating the moments of all the permitted configurations (cf. Williams, *Z. physikal. Chem.*, 1928, *A*, **138**, 75) that the theoretical moment of such a system is distinctly higher than that observed. However, one of the effects of resonance involving structures such as (II), with π-bonds between the oxygen and the ring, should be the restriction of rotation of the methoxy-groups about the C_{aryl}–O bonds. If such structures make an appreciable contribution to the hybrid, then the resonance effect and the steric effect are together able to account for the low moment observed. The former limits the possible configurations of each methoxy-group to two : the latter eliminates one of these, so that groups are constrained to lie *trans* to each other (Fig. 1).

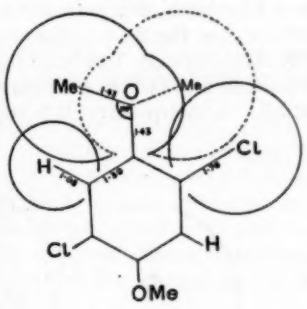


(II.)

This explanation was tested by measuring the dipole moment of 1 : 4-dimethoxynaphthalene. If it is correct, the moment of the compound should be up to $\sqrt{2}$ times that of quinol dimethyl ether, because the methoxy-groups would be constrained to lie *cis* to each other. However, the result is low—2·09 instead of the theoretical 2·45.

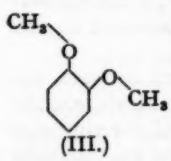
These facts indicate either that the groups cannot quite lie in the coplanar configurations, or that they are not rigidly fixed therein. The interference of the methyl groups with the β-hydrogen atoms, though much less than that with the *peri*-atoms, may prevent the methoxy-groups being completely coplanar, and cause them to be somewhat displaced upward or downward. Molecules in which each group is displaced one way would be polar, while those with the groups displaced in opposite directions would be non-polar. The two forms could be interchanged by thermal bombardment. On the other hand, the apparent polarity could be due to a torsional vibration about the C_{aryl}–O bonds, or, in other words, to an atom (or vibration) polarisation (see, *e.g.*, Sutton, *Ann. Reports*, 1940, **37**, 57).

FIG. 2.



If we assume that the methoxy-group moment is the same in naphthalene and in benzene ethers [the moments of 1-methoxynaphthalene and of anisole are equal (1·28)], then on the latter hypothesis we should have to suppose that the average amplitude of swing is approximately 32° for each group in 1 : 5-dimethoxynaphthalene and is 62° in 1 : 4-dimethoxy-naphthalene, while on the former hypothesis these same deflections would exist but would be permanent. On both, therefore, we should have to suppose that the tendency for the methoxy-groups to lie coplanar is less when there are two of them on one benzene ring than when there is only one. It may be, therefore, that when two methoxy-groups are on the *same* ring they reduce each other's π-bonding (see below).

A similar fixation of angular groups in the plane of an aromatic ring by a resonance mechanism has been postulated by Pauling ("Nature of the Chemical Bond," 2nd edn., Cornell, 1940, pp. 320 *et seq.*) to explain why the infra-red absorption spectra of *o*-chloro-, -bromo-, and -iodo-phenol contain two well-resolved peaks characteristic of O–H vibrations. Evidence of this fixation has also been obtained from dipole-moment studies by Anzilotti and Curran (*J. Amer. Chem. Soc.*, 1943, **65**, 607), who observed that the moments of *o*-chloro-, -bromo-, and -fluoro-anisole and of *o*-chlorophenetole in benzene solution (2·50, 2·47, 2·31, and 2·54) agree closely with the values (obtained from bond-moment data) for the *trans*-configurations of these molecules (2·50, 2·45, 2·37, and 2·50), but not with those for the *cis*- (0·47, 0·43, 0·35, and 0·47) or with those calculated on the basis of free rotation (1·82, 1·78, 1·71, and 1·82). These authors gave an explanation of their results similar to ours. On the other hand, both Mizushima, Morino, and Okazaki (*loc. cit.*) and Curran (*J. Amer. Chem. Soc.*, 1945, **67**, 1835) observe that the moment of veratrole does not agree with the value calculated for the *trans-trans*-configuration (III). The former authors find values in benzene of 1·32 at 40°, 1·24 at 25°, and 1·18 at 10°, and Curran finds 1·23 at 25° in dioxan. The calculated value for the *trans-trans*-configuration is about 0·6, and for the *cis-trans*-, 2·2 (cf. Curran, *loc. cit.*). In both papers it is postulated that resonance between the methoxy-groups and the ring is much reduced (relative to *o*-chloroanisole, etc.), but Curran tentatively offers also the alternative explanation that there is an appreciable number of *cis-trans*-molecules, in which, he points out, the distance from the carbon atom of one methoxy-group to the oxygen atom of the other is 1·7 A., corresponding to a strong hydrogen bond. Furthermore, Oesper, Smyth, and Kharasch (*J. Amer. Chem. Soc.*, 1942, **64**, 937) have found the dipole moment of 2 : 5-di-*tert.*-butylquinol dimethyl ether to be 1·47 ± 0·13 (recalculation by the method advocated by Halverstadt and Kumler, *loc. cit.*, gives 1·23 ± 0·02), though the *tert.*-butyl groups are quite large enough to eliminate one of the two coplanar configurations of each methoxy-group. These authors were indeed searching for just the effect which we think we have observed in 1 : 5-di-methoxynaphthalene; and because they did not find it they concluded that the π-bonding was too weak to hold the methoxy-groups coplanar. The chlorine atoms in 2 : 5-dichloroquinol dimethyl ether are also large enough to elimate one configuration (Fig. 2), but we observe that this compound is polar too ($\mu = 1{\cdot}03$).



(III.)

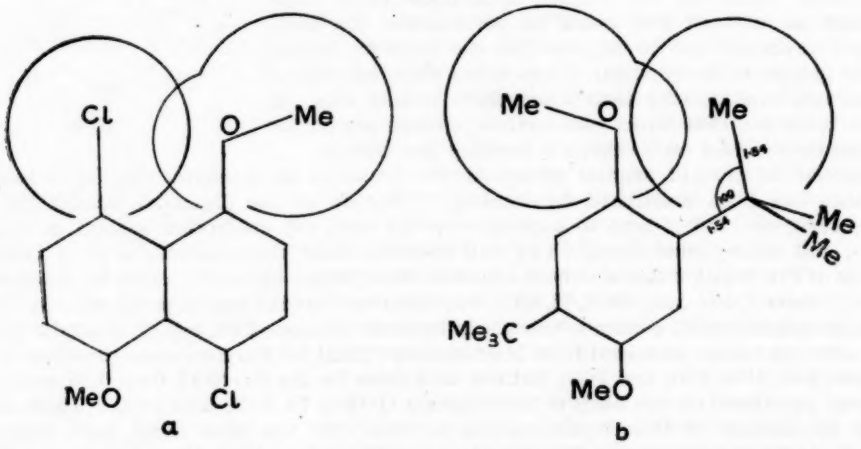
All these indications of less perfect fixation can be correlated with the presence of two methoxy-groups in one and the same ring; and they can therefore be explained on the

hypothesis that there is then a reduction of the π-bonding of each methoxy-group to the ring.

Clearly, however, no such hypothesis applies to 1 : 5-dimethoxynaphthalene. Also, in view of the observations on *o*-chloroanisole and similar compounds there is no reason to think that the additional polarity of 4 : 8-dichloro-1 : 5-dimethoxynaphthalene can be explained on such a basis. For this latter, a different explanation seems necessary.

A large atom polarisation has often been postulated to account for anomalous dipole moments, but on this occasion it is unlikely to be the true explanation. The differences between the total and the electron polarisations of the two symmetrical dichloronaphthalenes, 1 : 5 and 2 : 6, are each less than 1 c.c. Williams and Fogelberg, in obviously careful work (*J. Amer. Chem. Soc.*, 1931, **53**, 2096), found ${}_{T}P - {}_{E}P$ for the 2 : 6-isomer to be 0·1 c.c., whilst Weissberger and Sängewald found 0·8 c.c. (*Z. physikal. Chem.*, 1933, *B*, **20**, 145). Weissberger, Sängewald, and Hampson found ${}_{E}P$ for the 1 : 5-isomer to *exceed* ${}_{T}P$ by 5·7 c.c. (*loc. cit.*), but Weissberger and Hampson, in a painstaking repetition of their earlier work, found −0·2 c.c. for the 1 : 5- and 0·5 c.c. for the 2 : 6-compound. Nakata (*Ber.*, 1931, **64**, 2059; *Bull. Chem. Soc. Japan*, 1935, **10**, 318) reports 7·68 c.c. for the 2 : 6-isomer, but as he only makes measurements on two solutions and fails to extrapolate his polarisations to infinite dilution, his work is least acceptable of all. Consequently, it is reasonable to suppose that the contribution to the atom polarisation

FIG. 3.



made by the chlorine atoms in 4 : 8-dichloro-1 : 5-dimethoxynaphthalene is negligible. The contribution of the methoxy-groups should not be larger than the polarisation of 1 : 5-dimethoxynaphthalene (9·1 c.c.). The following hypothesis is therefore put forward to account for the anomaly.

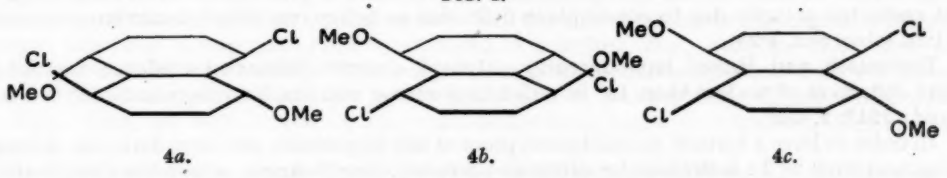
A scale diagram of the molecule shows that there is considerable interference between the oxygen atoms and the neighbouring chlorine atoms (Fig. 3*a*). The resulting strain can be relieved by movement of the substituents in two directions—one in the plane of the ring and one at right angles to it. A purely in-plane movement would not account for the moment observed, but an out-of-plane movement would give rise to an unsymmetrical (4*a* or 4*b*) as well as a symmetrical configuration (4*c*), and the former would possess a dipole moment.

It is not possible to form an exact estimate of the moment on the basis of this hypothesis, because of uncertainties in the atomic dimensions, particularly van der Waals radii, and in bond moments. Furthermore, nothing is known of the force field of the molecule, so it is impossible to say definitely (*a*) which bonds bend, by how much, and in what direction, and (*b*) what are the probabilities of each configuration, for if there is any kind of interaction between the groups at opposite ends of the naphthalene ring system, these probabilities need not be equal.

Nevertheless, a rough estimate has been made on the basis of the assumptions listed below and illustrated by Fig. 5. These are: (1) that the covalent and van der Waals radii have the values ascribed by Pauling (*op. cit.*, pp. 164, 189); (2) that the C–Cl bond moment effective in bending movements is −1·4; and that the corresponding component of the C–O–CH_3 group

along the C–O direction is +0·2; * (3) that the C–Cl and C–O bonds are equally deflected through an angle θ in a plane at right angles to that (plane A) containing the naphthalene rings before they are distorted; (4) that the methoxy-groups lie in planes B, B′ inclined at angles θ to plane A; (5) that the α, β, and central carbon atoms lie in four planes D, D′, D″, D‴ inclined at angles ½θ to plane A; (6) that each configuration 4*a* and 4*b* is half as probable as 4*c*, so that the moment of the mixture is $1/\sqrt{2}$ times that of 4*a* (or 4*b*).

FIG. 4.

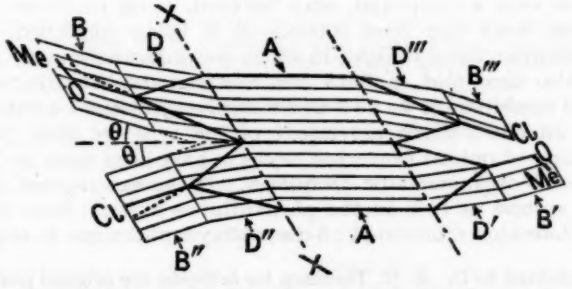


4*a*. 4*b*. 4*c*.

θ is calculated to be 33°, giving a polarisation of 29·4 c.c. According to a simple theorem, this can be added to the polarisation for the non-planarity of the methoxy-groups to give a total of 38·5 c.c. and a moment of 1·37 (observed, 0·95).

In the above treatment it has been assumed that the deflection is purely at right angles to plane A; and that no deflection occurs along the direction X–X. This is almost certainly an over-simplification. If we allow for deflection in the direction X–X by supposing that the force constants of the C–O and C–Cl bonds for deflection (*a*) in plane A, and (*b*) in the plane at right angles to it, are equal, another assumption is added to those already given, *viz.*, (3*a*) that the C–Cl and C–O bonds, having been deflected as defined in (3), are now deflected outwards through an angle ½θ in planes B, B′, B″, B‴. (The final positions of the groups are shown dotted on the left-hand side of Fig. 5.)

FIG. 5.



When this case is worked out, θ is found to be altered to 18°, and the theoretical moment to 1·0.

As indicated previously, assumption (6) may be an over-simplification too, for it appears from a spring-valency model that 4*a* and 4*b* are more stable than 4*c*, which would tend to make the observed moment greater than those calculated above: if the substance were completely in the polar configuration the theoretical limits would be 1·8 [assumption (3) alone] and 1·3 [assumptions (3) and (3*a*)]. On the whole, therefore, this hypothesis is more than adequate to account for the observed moment.

Tests of the Deflection Hypothesis.—If the above hypothesis is correct, we should expect that in 4 : 8-dibromo-1 : 5-dimethoxynaphthalene the bromine atoms would cause a larger out-of-

* These values are obtained by taking the σ-bond moment and half of the π-electron moment, *i.e.*, of that arising from conjugation of the group with the ring system. It would be inappropriate to take the whole of the latter into account because, although its positive pole is on the Cl or O atom, its negative pole is somewhere in the middle of the ring system, so it is not deflected so much as the σ-bond moment.

Furthermore, the appropriate σ-bond moment is that of the C–Cl or C–O–CH_3 grouping itself, and not the algebraic difference between this and the C–H bond moment (taken as 0·4, C$^-$H$^+$: cf. Bell, Thompson, and Vago, *Proc. Roy. Soc.*, 1948, **192**, *A*, 498). Accordingly, the correct σ-bond value for C–Cl is taken as −2·0 + 0·4 = −1·6; and to this is added 0·2, being about half of the π-bond moment, giving −1·4 as the net value of the moment which bends. The corresponding value for the methoxy-group is obtained from the moments of aliphatic ethers, anisole, *p*-chloroanisole, and chlorobenzene, and it is +0·2, with the negative pole toward the ring.

plane deflection than in the dichloro-compound, so the apparent moment should be larger. The observed moment are actually indistinguishable.*

It might appear that this hypothesis could explain the anomalous moment of 2 : 5-di-*tert.*-butylquinol dimethyl ether already mentioned (p. 2315), for the " radius " of the *tert.*-butyl groups is such as to give roughly as much overlap with the methoxy-oxygens as that of the chlorine atoms with the oxygens in the naphthalene compound (Fig. 3). If we suppose that the swinging of the methoxy-groups in the dibutyl ether contributes as much to the polarisation as does that in the 2 : 5-dichloro-compound, where there is practically no overlap (Fig. 2), and assess the polarity due to out-of-plane deflection as before, we obtain a maximum moment of 1·24 (observed, 1·23).

Bastiansen and Hassel have recently obtained electron-diffraction evidence for out-of-plane deflection of no less than 18° in *o*-dichlorobenzene and similar compounds (*Acta Chem. Scand.*, 1947, **1**, 489).

In order to have a further, unambiguous proof of this hypothesis, it is very desirable to take a compound such as 2 : 5-dichloro-(or dibromo-)-*p*-di-*tert.*-butylbenzene, where the complications caused by angular substituents should be absent. This is being attempted.

A completely different test was suggested by the nature of the distortion. It will be seen that the configurations 4*a* and 4*b* are not superimposable : they are mirror-images. Hence they are optically antimeric, and 4*c* is the corresponding internally compensated configuration. More generally, a suitable choice of X should enable a compound *peri*-di-X-naphthalene to be resolved, if the substituents are deflected out of the plane of the rings.

Difficulties were foreseen in preparing a suitable naphthalene derivative, but it was thought that these would be more easily surmountable in the phenanthrene system, in which there is even greater interference, in the 4- and the 5-positions. A still more favourable case appeared to be 3 : 4 : 5 : 6-dibenzphenanthrene, or the more easily prepared analogue, dinaphthopyridazine (IV), where the centre of one of the interfering hydrogen atoms in a scale diagram of the molecule is to be found in the bond joining the other hydrogen atom to the ring. It is difficult to see how such a compound, once resolved, could racemise.

(IV.)

After work had been started—it is being continued—on this problem, a preliminary communication came to light, in which Newman and Hussey (*J. Amer. Chem. Soc.*, 1947, **69**, 978; see also *idem*, *ibid.*, p. 3023, and Newman and Wheatley, *ibid.*, 1948, **70**, 1913) described the partial resolution of 4 : 5 : 8-trimethylphenanthrene-1-acetic acid, which owes its optical activity to an out-of-plane movement of the type we have postulated. The first suggestion of this source of optical isomerism seems to have been made by Porter (*J.*, 1938, 368) in connexion with some organometallic complexes. If the out-of-plane deflection is favoured in the naphthalene system as it is in the phenanthrene system, then the anomalous dipole moment of 4 : 8-dichloro-(or dibromo-)1 : 5-dimethoxynaphthalene is explained.

The authors are indebted to Dr. R. H. Thomson for bringing the original problem to their attention and for supplying materials, to Dr. J. A. Barltrop for affording useful advice, and to Imperial Chemical Industries Limited for a grant towards the cost of the investigation.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, December 22nd*, 1948.]

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491. *The Dipole Moments of Some Aliphatic Aldimines, with Special Reference to the Moment of the* C=N *Bond.*

By K. B. EVERARD and L. E. SUTTON.

The electric dipole moments of a series of aliphatic aldimines have been measured in order to provide a relatively reliable value for the C=N bond moment. This proves to be 1·4 D. The dipole moments vary from member to member of the series, and these variations are compared with those which have been reported in other homologous series.

The difference between aliphatic and aromatic values for the bond is also considered.

THERE does not appear to be any generally accepted value for the C=N bond moment in the literature. Smyth gives it as 0·9 D. (*J. Amer. Chem. Soc.*, 1938, **60**, 183), and Sutton as 2·4 D. (*Trans. Faraday Soc.*, 1934, **30**, 789). Bergmann and Weizmann (*Chem. Rev.*, 1941, **29**, 553)

* The orientation of this compound is known unambiguously, without the aid of dipole data, because the isomers are all known (Carter, Race, and Rowe, *J.*, 1942, 236).

attempt to calculate it from the dipole moment of benzophenone anil, using Sidgwick, Sutton, and Thomas's value (*J.*, 1933, 406) of 1·34 D. for the Ph–N: moment; but doubts have been cast on the correctness of the latter value by Bennett and Glasstone (*Proc. Roy. Soc.*, 1934, **145**, *A*, 71), who substitute 0·21 D. for it; and in any case, the moment of such an aldimine, with benzene rings attached, is liable to be altered by resonance. The estimate 2·27 D. of the C=N bond moment derived therefrom is consequently of doubtful validity.

Aliphatic aldimines offer the advantages of simplicity in preparation and the lack of complications (such as mesomeric moments) in evaluating the bond moment. They show tautomerism similar to keto-enol tautomerism, but the concentration of the enamine form in aliphatic aldimines is negligible (von Auwers and Wunderling, *Ber.*, 1932, **65**, 70). They are not, however, stable substances. They are prone to aerial oxidation (Chancel, *Bull. Soc. chim.*, 1894, **11**, 933); the simpler ones are apt to polymerise to cyclic trimers (Henry, *Bull. Acad. roy. Belg.*, 1895, **29**, 489); others undergo aldol-like condensations (Kharasch, Richlin, and Mayo, *J. Amer. Chem. Soc.*, 1940, **62**, 494).

These difficulties were met in a way described in the experimental section, but even so, it was found that the " scatter " of measurements was somewhat more than that encountered with more stable compounds. This, however, is taken into account in estimating the error of each moment. The entire preparation and measurement of one compound were repeated, and the two values differed by only 0·01 D. The purity of each compound was assessed by analysis, the results of which, however, are not of course affected by polymerisation. Some of the lower members of the series polymerise too readily to make examination worth while (Henry, *loc. cit.*).

Experimental.

(Analyses by Mr. F. C. Hall.)

The method used for the preparation of these aldimines was essentially that of Campbell, Sommers, and Campbell (*J. Amer. Chem. Soc.*, 1944, **66**, 82). The aldehydes and amines used as starting materials were B.D.H. specimens, except for acetaldehyde and ethylamine. Acetaldehyde was distilled before use; ethylamine was liberated from its hydrochloride by alkali, dried, and condensed in a spiral cooled with solid carbon dioxide.

The first aldimine so prepared, n-*butylidene*iso*butylamine*, was twice distilled under atmospheric pressure using a 4-in. Dufton column. The product gave an unsatisfactory analysis, however, so all the other aldimines (and subsequently this one too) were distilled under reduced pressure without an air-leak in the Claisen flask, and were analysed and used within 24 hours.

All the aldimines became yellow when kept for periods of a few hours to a few days. The fractional redistillation of those affected the most was carried out in several parts immediately before solutions were made up for polarisation measurements.

The average yield of purified material was about 50%.

B. p.s and analytical results are entered in Table I.

Table I.

Aldehyde residue.	Amine residue.	B. p.	Pres. (mm.).	Found, %. C.	H.	N.	Calc., %. C.	H.	N.
n-Bu	*iso*-Am	61°	20	76·8	13·5	10·1	76·6	13·5	9·9
n-Bu	*iso*-Bu	142·5 *	(1) atm.	75·6	13·5	11·2 (2)	75·6 †	13·4 †	11·0 †
		35	(2) 11						
n-Bu	*n*-Bu	56	29	75·6	13·5	11·0	75·6	13·4	11·0
n-Bu	*iso*-Pr	30	29	74·2	13·3	12·5	74·3	13·3	12·4
n-Bu	*n*-Pr	46	39	74·4	13·5	12·4	74·3	13·3	12·4
n-Bu	Et	50	134	72·4	13·0	12·8	72·7	13·1	14·1
Pr	*n*-Bu	54	65	73·9	13·5	12·6	74·3	13·3	12·4
Et	*n*-Bu	51	121	—	—	14·3	—	—	14·1

* Corrected. † Required values (new compound).

The purification of benzene and the physical measurements were carried out as described in the preceding paper. All dipole moments are given in Debye units.

Results.

ω_2.	ε_{12}.	v_{12}.	$-\Delta n$.	ω_2.	ε_{12}.	v_{12}.	$-\Delta n$.
			n-Butylidene*iso*amylamine.				
0·004626	2·2808	1·1458	0·00059	0·018824	2·3019	1·1480	0·00232
0·007052	2·2840	1·1461	0·00089	0·019080	2·3026	1·1481	0·00233
0·011882	2·2907	1·1468	0·00147				

$\varepsilon_{12} = 2{\cdot}2734 + 1{\cdot}511\omega_2$; $v_{12} = 1{\cdot}1450 + 0{\cdot}157\omega_2$; $\Delta n = -0{\cdot}00004 - 0{\cdot}121\omega_2$;
${}_TP_2 = 95{\cdot}04$ c.c.; ${}_EP_2 = 44{\cdot}64$ c.c.; $\mu = 1{\cdot}57 \pm 0{\cdot}05$.

ω_2.	ε_{12}.	v_{12}.	$-\Delta n$.	ω_2.	ε_{12}.	v_{12}.	$-\Delta n$.
			n-Butylidene*iso*butylamine (1).				
0·003222	2·2767	1·1459	0·00040	0·009579	2·2875	1·1470	0·00132
0·008000	2·2856	1·1468	0·00111	0·016148	2·2980	1·1482	0·00210

$\varepsilon_{12} = 2·2719 + 1·634\omega_2$; $v_{12} = 1·1454 + 0·177\omega_2$; $\Delta n = -0·00002 - 0·131\omega_2$;
${}_{T}P_2 = 89·32$ c.c.; ${}_{E}P_2 = 40·20$ c.c.; $\mu = 1·55 \pm 0·03$.

n-Butylidene*iso*butylamine (2).

0·002303	2·2767	1·1452	0·00033	0·014258	2·2966	1·1474	0·00193
0·004797	2·2815	1·1456	0·00066	0·015564	2·2978	1·1477	0·00203

$\varepsilon_{12} = 2·2733 = 1·598\omega_2$; $v_{12} = 1·1447 + 0·190\omega_2$; $\Delta n = -0·00003 - 0·131\omega_2$;
${}_{T}P_2 = 88·84$ c.c.; ${}_{E}P_2 = 40·59$ c.c.; $\mu = 1·54 \pm 0·03$.

n-Butylidene-*n*-butylamine.

0·007287	2 2852	1·1464	0·00094	0·016599	2·3005	1·1483	0·00202
0·011180	2·2926	1·1472	0·00139	0·018202	2·3062	1·1485	0·00231
0·012066	2·2938	1·1474	0·00152				

$\varepsilon_{12} = 2·2719 + 1·819\omega_2$; $v_{12} = 1·1451 + 0·188\omega_2$; $\Delta n = -0·00004 - 0·122\omega_2$;
${}_{T}P_2 = 94·17$ c.c.; ${}_{E}P_2 = 41·22$ c.c.; $\mu = 1·61 \pm 0·03$.

n-Butylidene*iso*propylamine.

0·002612	2·2792	1·1454	0·00031	0·008602	2·2913	1·1466	0·00125
0·003803	2·2816	1·1454	0·00050	0·010820	2·2959	1·1474	0·00154

$\varepsilon_{12} = 2·2739 + 2·022\omega_2$; $v_{12} = 1·1446 + 0·240\omega_2$; $\Delta n = 0·00008 - 0·151\omega_2$;
${}_{T}P_2 = 89·74$ c.c.; ${}_{E}P_2 = 36·45$ c.c.; $\mu = 1·61 \pm 0·01$.

n-Butylidene-*n*-propylamine.

0·002642	2·2778	1·1452	0·00036	0·010027	2·2921	1·1469	0·00135
0·004692	2·2824	1·1459	0·00064	0·014058	2·2994	1·1477	0·00190

$\varepsilon_{12} = 2·2732 + 1·867\omega_2$; $v_{12} = 1·1448 + 0·207\omega_2$; $\Delta n = 0·00000 - 0·135\omega_2$;
${}_{T}P_2 = 85·35$ c.c.; ${}_{E}P_2 = 36·45$ c.c.; $\mu = 1·55 \pm 0·02$.

n-Butylidene-ethylamine.

0·003878	2·2826	1·1460	0·00056	0·009530	2·2964	1·1473	0·00135
0·005732	2·2866	1·1463	0·00082	0·012804	2·3057	1·1480	0·00185

$\varepsilon_{12} = 2·2721 + 2·594\omega_2$; $v_{12} = 1·1452 + 0·219\omega_2$; $\Delta n = 0·00000 - 0·144\omega_2$;
${}_{T}P_2 = 88·78$ c.c.; ${}_{E}P_2 = 31·73$ c.c.; $\mu = 1·67 \pm 0·05$.

Propylidene-*n*-butylamine.

0·004614	2·2818	1·1460	0·00063	0·011016	2·2955	1·1470	0·00148
0·007546	2·2877	1·1466	0·00099	0·016104	2·3054	1·1482	0·00216
0·009976	2·2921	1·1469	0·00133				

$\varepsilon_{12} = 2·2722 + 2·059\omega_2$; $v_{12} = 1·1452 + 0·178\omega_2$; $\Delta n = 0·00001 - 0·134\omega_2$;
${}_{T}P_2 = 88·56$ c.c.; ${}_{E}P_2 = 35·43$ c.c.; $\mu = 1·61 \pm 0·02$.

Ethylidene-*n*-butylamine.

0·003896	2·2829	1·1457	0·00055	0·009741	2·2964	1·1468	0·00134
0·006647	2·2882	1·1461	0·00097	0·012905	2·3043	1·1474	0·00179

$\varepsilon_{12} = 2·2730 + 2·408\omega_2$; $v_{12} = 1·1450 + 0·188\omega_2$; $\Delta n = -0·00003 - 0·135\omega_2$;
${}_{T}P_2 = 84·83$ c.c.; ${}_{E}P_2 = 31·44$ c.c.; $\mu = 1·61 \pm 0·03$.

Discussion.

The results in Table II show a variation in the moments of these aldimines, albeit a small one (no two moments lie more than 0·12 apart). Similar variation has been observed in a number of other homologous series which have been investigated [see tables given by Wheland (" The Theory of Resonance," Wiley, 1944, p. 123) and by Groves and Sugden (*J.*, 1937, 158)].

Table II.

Aldehyde residue.	Amine residue.	Moment.	Uncertainty (±).
n-Butylidene	*iso*Amylamine	1·57	0·05
,,	*iso*Butylamine	1·55, 1·54	both 0·03
,,	*n*-Butylamine	1·61	0·03
,,	*iso*Propylamine	1·61	0·01
,,	*n*-Propylamine	1·55	0·02
,,	Ethylamine	1·67	0·05
Propylidene	*n*-Butylamine	1·61	0·02
Ethylidene	,,	1·61	0·03

Changing the aldehyde residue appears not to affect the moment: this may seem strange in view of variations of up to 0·4 in, for example, the alkyl halide series, but Cowley and Partington (*J.*, 1935, 604) have found that the moments (in solution) of the somewhat analogous *n*-butyl, *n*-propyl, and ethyl cyanides are all 3·57 (though that of methyl cyanide is 0·13 lower). The moments (in solution) of another similar series, the aldehydes, vary only from 2·49 for acetaldehyde to 2·60 for *iso*valeraldehyde (Coomber and Partington, *J.*, 1938, 1444), whilst those measured in the gas phase of acetaldehyde (2·72), propaldehyde (2·73), and *n*-butaldehyde (2·72) are sensibly the same (Hurdis and Smyth, *J. Amer. Chem. Soc.*, 1943, **65**, 89). It is hoped to perform gas-phase measurements on the aldimines for comparison with the latter work.

As the size of the amine residue is increased, the moment tends to diminish (though the *n*-propyl compound is irregular); this trend might be expected if it is due to the greater polarisability of the higher alkyl groups, for an increase in the N–R moment in the grouping C–N=R not only partly opposes the resultant moment of the system, but also results in the nitrogen atom becoming less electronegative, which should diminish the C=N bond moment.

The chief peculiarity seems to be the effect of chain branching, which appears to cause a decrease in moment of 0·06 when the alkyl residue is butyl, and an increase of 0·06 when it is propyl. The same thing is evident in the chloride series where the changes are minus and plus 0·05 (Wiswall and Smyth, *J. Chem. Physics*, 1941, **9**, 356). The reason for this is obscure, but, as it may conceivably be a result of measuring these dipole moments in solution, discussion is deferred until some measurements in the gas phase have been carried out.

Despite these variations, we can give a better estimate than any hitherto of the C=N bond moment.

It is necessary to know the values of the H–C and C–N bond moments. Those of bonds between any element and quadrivalent carbon, as usually evaluated, depend necessarily on the former moment, which must therefore be considered first. There seems to be fairly general agreement that its magnitude is 0·3—0·4, but there has been some controversy recently as to its direction, following Coulson's statement (*Trans. Faraday Soc.*, 1942, **38**, 433) on the basis of some wave-mechanical calculations that the positive pole was situated nearer the carbon atom. It had previously been assumed that the opposite was the case, as the greater electronegativity of carbon would require. Coulson included for the first time in a bond moment the effect of sp^3 hybridisation of the bonding orbitals of carbon, which results in a lop-sided distribution of the negative charge constituting each bond.

This emphasises the rather arbitrary nature of the definition of a bond moment. Such a moment arises partly from the atomic dipole as above, partly from the covalent dipole, and partly from the ionic dipole (for references, see, *e.g.*, Cottrell and Sutton, *Quart. Reviews*, 1948, **2**, 260). The relevant definition is really determined by the nature of the observation; and the fact that in bending movements of certain benzene compounds the moving H–C dipole has its positive pole towards the hydrogen (Bell, Thompson, and Vago, *Proc. Roy. Soc.*, 1948, **192**, *A*, 498) suggests that for many purposes a definition excluding the atomic dipole is more useful. We shall use this in the present context, and so take the H–C dipole to be H^+C^- and of magnitude 0·4.

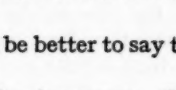
As for the C–N bond moment, Hammick, New, and Sutton (*J.*, 1932, 742) have given 1·2 for the moment of the grouping CH_3–N, obtained vectorially from the moments of ammonia and methylamine; assuming that the methyl group moment ($= \mu_{H-C}$) is 0·4, this gives $\mu_{C-N} = 0{\cdot}80$. Bennett and Glasstone (*loc. cit.*) give 0·71 for the CH_3–N moment, corresponding to a C–N bond moment of 0·31. Smyth quotes the latter as 0·45 (*loc. cit.*). This value will be taken as the most probable, because it agrees with that which can be calculated from a recent determination of the trimethylamine moment, 0·86 (benzene solution; Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374). Since the valency angles are tetrahedral, or nearly so [electron-diffraction work on trimethylamine gives the value 108° ± 4° for the C–N–C bond angle (Brockway and Jenkins, *J. Amer. Chem. Soc.*, 1936, **58**, 2036); *X*-ray diffraction in the vapour phase gives 110° (Richter, *Physikal. Z.*, 1935, **36**, 85)], this must be the CH_3–N moment, so on this basis the C–N moment is 0·46.

The –C= and =N– angles in aldimines have not been determined, but it will be assumed that they are each 120°. This has been confirmed in the case of some molecules having ethylenic carbon atoms (see, *e.g.*, Gallaway and Barker, *J. Chem. Physics*, 1942, **10**, 88) and of a few molecules containing doubly-bound nitrogen [*e.g.*, Robertson finds the =N– angles in *trans*-azobenzene to be 121° (*J.*, 1939, 232), and Hughes finds 120° in dicyandiamide (*J. Amer. Chem. Soc.*, 1940, **62**, 1258), both by *X*-ray diffraction methods].

It may be assumed that the alkyl groups are disposed in the *trans*-configuration about the double bond in aliphatic aldimines, as is found with benzylideneaniline (de Gaouck and Le Fèvre, *J.*, 1938, 741). Thus if the alkyl group moments, being opposed, cancel, we are left with three bond moments, H–C, C=N, and N=C, which have a resultant of 1·54—1·67. The direction of the C=N bond moment may be assumed to be the same as that of the C–N and C≡N moments (*i.e.*, C^+N^-); so its evaluation consists in the solution of a vector quadrilateral. A trigonometrical solution gives the values 1·38 and 1·52 for the C=N bond moment, according as the lowest or highest aldimine moment is taken, or 1·44 from the arithmetic mean, 1·59, of all the aldimine moments.

This bond moment may be compared with those of C–N (0·45) and C≡N (3·2 from solution measurements, 3·6 from gas). The moments of carbon–nitrogen bonds evidently do not rise linearly with the multiplicity as do the energies (Pauling, " Nature of the Chemical Bond," Cornell, 2nd ed., 1940, pp. 53, 131); on the contrary, the difference between the triple and the double bond moments markedly exceeds that between the double and the single. This may be because the C≡N bond owes its large polarity chiefly to the atomic dipole provided by the unshared electrons on the nitrogen (see Coates and Sutton, *J.*, 1948, 1187). If this be so, it lends weight to Cowley and Partington's explanation (*loc. cit.*) of the fact that, despite the large polarising power of the cyanide group, alkyl cyanides higher than methyl have the same moment: they suggested that this was due to the location of the dipole far away from the attached alkyl groups.

The C=N bond moment is a little more than half as polar as the C=O (2·4), and the same is true of the single bond moments. This parallels the electronegativity differences of carbon and nitrogen and of carbon and oxygen, which are in the approximate ratio of 1 : 2.

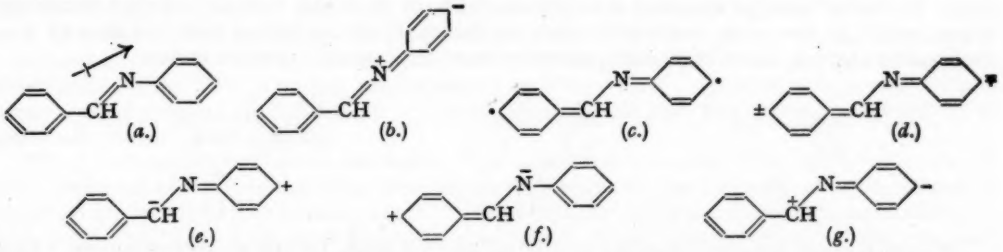
It is noteworthy that the indication given by the present work, of the decrease in the polarity of the C=N bond with increase in the molecular weight of the amine, and a statement by Coates and Sutton (*loc. cit.*) that " . . .thermal data suggest that the C=N bond heat of formation will be large in imines only when it has large alkyl groups attached," may appear to be related by a principle enunciated by Walsh (*J.*, 1948, 398), that the more polar a bond is the weaker it is. Both the moment attributed to the C=N bond and its heat of formation are, however, residual, formal values. It would be better to say that the moment of the  grouping decreases when its heat of formation increases. Our view of the former change is that it is due to one bond increasing in polarity while another decreases; and we cannot attribute the latter change to any one bond. Such a comparison, therefore, does not provide unambiguous support for Walsh's principle.

The moment of the C=N bond in aromatic aldimines might perhaps be expected to differ from that found above. We must, however, be quite clear what we mean by it. It may be defined in two ways: (1) That moment which, when vectorially added to the H–C bond moment, the Ph–N σ-bond moment *, and the total mesomeric moment, gives the correct magnitude and direction to the observed moment of the molecule; this definition gives a quantity which excludes the mesomeric effect; it therefore closely corresponds to the thermochemical quantity, bond energy term, and like it should be constant. It may be distinctively labelled the *bond moment term*. (2) That moment which gives the observed total moment when vectorially added to that of the H–C bond and to one in the direction of the Ph–N bond which is the algebraic sum of the Ph–N σ-bond moment and such mesomeric moment as there is in this line. This quantity might throw light on the actual electronic state of the C=N bond in this particular molecule; it would be expected to vary from one molecule to another, and it might be relevant to any relation between bond moment and local bond properties.

The direction of the benzylideneaniline moment can be got from the moments of this substance (1·57) and of either *p*-chlorobenzylideneaniline (1·77) or *p*-chlorobenzylidene-*p*-toluidine (2·06) (de Gaouck and Le Fèvre, *loc. cit.*) with either chlorobenzene (1·55) or *p*-chlorotoluene (calculated as 1·95): the two values agree within 2°. We need next to know the directions of all the bonds, the moment of the H–C bond and, for definition (1) above, the direction of the mesomeric moment in the molecule as a whole and the σ-bond moment of Ph–N (*i.e.*, excluding mesomeric moment). We assume as before that bonds around the carbon and nitrogen atoms have regular trigonal symmetry, that the H–C and Ph–N σ-bond moments

* This excludes the C–H bond moment of the Ph group because it is balanced by that in the other Ph group.

are 0·4 and 0·45 respectively, and that the direction * of the mesomeric dipole is from either of the central atoms to approximately the centre of the remote benzene ring (see below). The vector polygons are then solved. We find that by definition (1) the C=N moment is 1·06 and the mesomeric moment is 0·68 in the sense shown over structure (*a*); by definition (2) the former is 1·30.



The justification for ascribing the above direction to the mesomeric moment is the following. Coates and Sutton (*loc. cit.*) have pointed out that a structure of type (*b*) would be unimportant in benzylideneaniline because it would require the molecule to be differently shaped; so contributions from it must be ignored, though they would assist in explaining the sign of the mesomeric moment. The important types of structure are likely to be (*a*), (*c*), (*d*), (*e*), (*f*), and (*g*), of which (*a*), (*c*), and (*d*) make no contribution to the mesomeric moment; (*e*) would give a moment in the opposite sense to that observed; and (*f*) and (*g*) would give the observed sense. It is inferred that (*f*) and (*g*) together are more important contributors to the hybrid than (*e*), as would be expected from the electronegativity of nitrogen being greater than that of carbon.

When structures with charges on the *ortho*-positions are also taken into account, it appears that the most likely position of a mesomeric charge centroid in a ring is at about the centre; but there is some uncertainty in this, hence in the direction of the mesomeric moment, and so in the moments we have given under definition (1). We estimate this uncertainty to be $\pm 0{\cdot}1$.

The apparent reduction of the C=N bond moment term in benzylideneaniline from the pure double-bond value (1·44) towards that of the pure single bond (0·45) must be due to some other cause than mesomerism (the effect of which has been separately assessed). This cause is probably to be sought in the different states of hybridisation of the bond orbitals in the aliphatic and aromatic molecules. It is noteworthy that the bond energy term of this C=N bond (96 kcals.) is also reduced from the pure double-bond value (106) towards that of the pure single bond (52·5) (Coates and Sutton, *loc. cit.*).

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PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, December 22nd*, 1948.]

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492. *Studies in the Azole Series. Part XIX. Reactions with 2-Mercaptothiazol-5-one.*

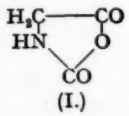
By J. D. BILLIMORIA and A. H. COOK.

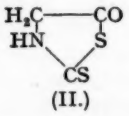
Anhydro-*N*-carboxyglycine (I) proved too labile for use in projected condensation reactions but its dithio-analogue (II) was readily converted into a variety of condensation products of type (III). Products (III) were converted into α-amino-acids either directly or through the analogue of (II) of general formula (V), the constitution of representatives of which were confirmed by their preparation from α-amino-acids.

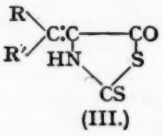
ANHYDRO-*N*-CARBOXYGLYCINE (I) (Leuchs, *Ber.*, 1906, **39**, 857; Go and Tani, *Bull. Chem. Soc. Japan*, 1939, **14**, 510) has been used in the preparation of polyglycine, whilst the analogous 2-mercaptothiazol-5-one [or a tautomeric form, 2-thiothiazolid-5-one] (II) (Cook, Heilbron, and Levy, *J.*, 1948, 201) is a useful intermediate in the preparation of simple peptides of known constitution (Sir Ian Heilbron, this vol., p. 2099). Compound (II) has also provided

* This is not an assumption of the *sense* of the moment but only that the moment acts in one or other sense in the direction of this line.

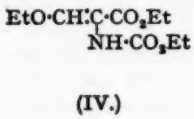
a route to an analogue of penicillamine (Billimoria, Cook, and Heilbron, this vol., p. 1437) and to α-amino-β-thiol-acids generally (unpublished work). The same compound (II) had virtually been condensed with benzaldehyde or with ethyl orthoformate in an acid medium (Cook, Heilbron, and Levy, *loc. cit.*) to give the products (III; R = H, R′ = Ph; R = H, R′ = OEt, respectively), thus demonstrating the presence of a reactive methylene group in (II). It seemed possible therefore that (II) and perhaps (I) might, with appropriate treatment, prove useful in the ways indicated below in the synthesis of higher amino-acids and near derivatives thereof, and the present paper described experiments to these ends.


(I.)


(II.)


(III.)

It soon became apparent that the ring of (I) was too labile for the present purposes. Thus with alcoholic hydrogen chloride anhydrocarboxyglycine was quantitatively converted into glycine ethyl ester hydrochloride, and alcoholic sodium ethoxide opened the ring in a similar manner but with partial polymerisation. Again, on treatment with morpholine (I) afforded *glycine morpholide* which was further characterised as its *picrate*. Under similar conditions glycine ethyl ester reacted with (I) to give glycylglycine ethyl ester in poor yield, and it seemed unprofitable to attempt the preparation in this manner of other peptides in useful yield. The compound (I) failed to condense with benzaldehyde under a variety of conditions, though it reacted with ethyl orthoformate undergoing condensation and simultaneous ring-fission with the formation of an unsaturated compound, possibly (IV). Clearly the methylene group of (I) was not as reactive as was desired.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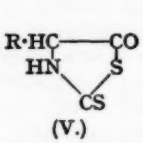
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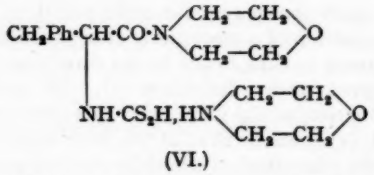
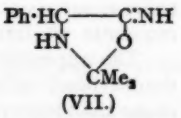

(VI.)


(VII.)

By contrast with (I), the 2-mercaptothiazol-5-one (II) was found to condense readily with a wide variety of aldehydes, ketones, or acetals or ketals thereof, in presence of a basic catalyst, to give compounds of the type (III). The *4-ethylidene* (III; R = Me, R′ = H), *methylthioethylidene* (III; R = CH_2·SMe, R′ = H), n-*butylidene* (III; R = Pr^n, R′ = H), iso*butylidene* (III; R = Pr^i, R′ = H), *iso*propylidene (III; R = R′ = Me), benzylidene (III; R = Ph, R′ = H), and o- and p-*hydroxybenzylidene* (III; R = C_6H_4·OH, R′ = H) compounds were obtained.

Attempts to reduce representative compounds of those mentioned immediately above with reagents such as iron and hydrochloric acid, magnesium and alcohol, titanous chloride in acid solution, or calcium in acetic acid were unsuccessful. However, zinc dust in presence of acetic acid was more effective and the benzylidene compound was readily reduced in this manner to *2-thio-4-benzylthiazolid-5-one* (V; R = CH_2Ph). The latter, the first analogue of the parent compound (II) to be described, was characterised by its reaction with morpholine to give the *morpholinium* salt of *N*-dithiocarboxy-β-phenylanaline morpholide (VI). On treatment with hydrochloric acid (VI) reverted to (V; R = CH_2Ph), just as carbamidomethyldithiocarbamates afforded (II) on acidification (cf. Cook, Heilbron, and Levy, *loc. cit.*). Finally, when (V; R = CH_2Ph) was treated with methanolic sodium methoxide, followed by methanolic hydrogen chloride, the hydrochloride of β-phenylalanine methyl ester was obtained. The series of reactions thus virtually provides a novel route to phenylalanine.

The structure of the compound formulated as (V; R = CH_2Ph) was established by its synthesis from β-phenylalanine. The methyl ester of the amino-acid was converted into the amide and thence with carbon disulphide into a salt of the corresponding dithiocarbamic acid. On acidification of its solution the latter compound was converted into the compound obtained previously. This method of obtaining 2-thiothiazolid-5-ones seems to be of general applicability and was used to prepare the analogue (V; R = Ph).

α-Aminobenzyl cyanide condensed with acetone in presence of sodium methoxide to give *5-imino-4-phenyl-2 : 2-dimethyloxazolidine* (VII) (cf. the similar behaviour of aminoacetonitrile;

Cook, Heilbron, and Levy, *loc. cit.*), which on treatment with water was converted into α-amino-phenylacetamide. The sodium *N*-dithiocarbamate derived from the latter yielded, on acidification, *2-thio-4-phenylthiazolid-5-one* (V; R = Ph). The new compound behaved like its analogues, reacting with morpholine to give the *morpholinium* salt (cf. VI).

2-Thio-4-*p*-hydroxybenzylidene- and -4-*cyclo*hexylidene-thiazolid-5-one (Billimoria, Cook, and Heilbron, Part XVI, this vol., p. 1437) were also reduced by zinc dust in acetic acid to *2-thio-4-p-hydroxybenzyl-* and *-4-cyclohexyl-thiazolid-5-one*, respectively, but similar treatment of (III; R = CH_2·SMe, R′ = H) led to its losing the methylthio-group, and *2-thio-4-ethylthiazolid-5-one* (V; R = Et) was obtained in small yield. This structure was certain because on treatment with ethanolic hydrogen chloride the ring was opened to afford ethyl α-aminobutyrate hydrochloride.

When representative 2-thio-4-alkylidene- and -arylidene-thiazolid-5-ones were reduced with red phosphorus and hydrogen iodide, simultaneously the ring was opened with loss of the elements of carbon disulphide to give α-amino-acids. β-Phenylalanine, tyrosine, valine, leucine, norleucine, and *cyclo*hexylglycine were so obtained in good yield, whilst even methionine was obtained in small quantity by reducing (III; R = CH_2·SMe, R′ = H). α-Aminobutyric acid prepared in this manner from (III; R = Me, R′ = H) was esterified to give ultimately the ester hydrochloride identical with that obtained from (V; R = Et) as described above. In view of the facility with which (II) may be condensed with carbonyl compounds, and the ease of reductive fission of the condensation products (III), these reactions appear to provide useful new routes to α-amino-acids.

Experimental.

Reactions of Anhydrocarboxyglycine.—This compound (Go and Tani, *Bull. Chem. Soc. Japan*, 1939, **14**, 510) did not melt at 100° as described but evolved carbon dioxide at that temperature and gave thus an amorphous infusible residue. It was more conveniently crystallised from anhydrous acetone and could be partly sublimed in a high vacuum to give colourless needles.

(*a*) The anhydride (0·5 g.) was kept in saturated alcoholic hydrogen chloride (10 c.c.) at 0°. After ½ hour the mixture was warmed until dissolution of the compound was complete. On cooling and addition of a little ether, glycine ethyl ester hydrochloride was obtained, having m. p. 144°, undepressed on admixture with an authentic specimen prepared from glycine.

(*b*) The anhydride (0·5 g.) was kept at 0° with ethanolic sodium ethoxide (10 c.c.) containing sodium (0·13 g.). A solid (polymeride?) which separated was removed. The filtrate was titrated with 5N-ethanolic hydrogen chloride, until just acid to phenolphthalein; the sodium chloride which separated was filtered off, and on addition of a little ether to the filtrate glycine ethyl ester hydrochloride was again obtained, having m. p. and mixed m. p. with an authentic specimen 144°.

(*c*) The anhydride (0·51 g.) was kept with water (20 c.c.) for 4 hours at 15°. The anhydride gradually dissolved, and a trace of precipitate was filtered off. The filtrate on evaporation *in vacuo* yielded glycine which was identified as its picrate.

(*d*) The anhydride (0·5 g.) was suspended in water (20 c.c.) at 40°. After some time, a precipitate was obtained which was insoluble in most organic solvents and resembled the compound described by Go and Tani (*loc. cit.*), namely a polyglycine.

(*e*) The anhydride (0·5 g.), dissolved in ethyl acetate, was treated at 40° with a number of bases in equivalent amounts. Ethylamine, aniline, benzylamine, *p*-toluidine, and triethylamine were used. In each case a polymeric product was obtained which could not be crystallised from organic solvents.

Glycine Morpholide.—Anhydrocarboxyglycine (5 g.) was dissolved in acetone (150 c.c.), the solution cooled to 0°, and morpholine (6 g.), dissolved in acetone (30 c.c.) and pre-cooled to 0°, was added. After 20 minutes at 0° the solution was kept overnight at room temperature. It was finally heated under reflux for a few minutes, a trace of precipitated polymeride filtered off, the filtrate concentrated *in vacuo*, and the residual oil distilled at 0·5 mm. whereupon partial decomposition occurred and a fraction, b. p. 120—130° (2·5 g.), was collected. On refractionation, *glycine morpholide* (2 g.) was obtained as a pale yellow oil, b. p. 128—130°/0·5 mm. (Found: C, 50·55; H, 8·4; N, 19·0. $C_6H_{12}O_2N_2$ requires C, 50·05; H, 8·35; N, 19·45%). The compound was characterised by the preparation, in ethyl acetate, of the *picrate*, which crystallised from alcohol in pale yellow needles, m. p. 222—224° (decomp.) (Found: C, 38·5; H, 4·05. $C_{12}H_{15}O_9N_5$ requires C, 38·6; H, 4·0%).

Glycylglycine Ethyl Ester.—Anhydrocarboxyglycine (5 g.) was dissolved in acetone (150 c.c.) and cooled to 0°. Glycine ethyl ester (7 g.), also dissolved in acetone (20 c.c.) and cooled to 0°, was added dropwise to the solution of the anhydride with stirring. The mixture was kept for ½ hour at 0° and overnight at room temperature and finally heated under reflux for a few minutes. A trace of precipitated polymeride was filtered off, the solvent removed *in vacuo*, and the residual oil distilled at 100° in a high vacuum. Considerable decomposition occurred, and the colourless viscous distillate solidified with some difficulty. On recrystallisation from alcohol–ethyl acetate, colourless needles (Found: N, 17·55. Calc. for $C_6H_{12}O_3N_2$: N, 17·5%), m. p. 85°, undepressed on admixture with authentic glycylglycine ethyl ester, were obtained. The m. p. of its hydrochloride was not depressed by glycylglycine ethyl ester hydrochloride.

Condensation of Anhydrocarboxyglycine with Ethyl Orthoformate.—The anhydride (5 g.), ethyl orthoformate (18 c.c.), and acetic anhydride (15 c.c.) were heated on the water-bath for 1 hour with occasional stirring, until a clear solution was obtained. A trace of amorphous matter which soon separated was rejected and the filtrate was concentrated *in vacuo* to give a crystalline mass contaminated with a syrupy mother-liquor. This was treated with light petroleum (200 c.c.) and chloroform

(10 c.c.), whereupon the crystals dissolved and the syrup deposited a dark amorphous powder which was rejected. The filtrate, when kept at 0° for some hours, deposited long colourless needles (1·25 g.). On recrystallisation from benzene–light petroleum, colourless plates of (?) *ethyl α-carbethoxyamino-β-ethoxyacrylate*, m. p. 92°, were obtained (Found: C, 51·0; H, 7·2. $C_{10}H_{17}O_5N$ requires C, 51·0; H, 7·6%). The compound was very unstable and decomposed within a day even under nitrogen.

2-*Thio*-4-*ethylidenethiazolid*-5-*one*.—(*a*) 2-Mercaptothiazol-5-one (Cook, Heilbron, and Levy, *loc. cit.*) (4 g.) was dissolved in warm ethyl acetate (75 c.c.), and a large excess of freshly distilled acetaldehyde (12 c.c.) was added. Piperidine (2 drops) was added and the solution kept at room temperature for several days. A crop of large straw-coloured plates which separated was filtered off and further crops were obtained by concentrating the mother-liquor. The combined yield (3 g.) of the *ethylidene* compound recrystallised from glacial acetic acid in straw-coloured plates, m. p. 195—196° (Found: C, 38·0; H, 3·4; S, 40·4. $C_5H_5ONS_2$ requires C, 37·8; H, 3·2; S, 40·3%).

(*b*) 2-Mercaptothiazol-5-one (5 g.) was dissolved in boiling glacial acetic acid (50 c.c.), and acetaldehyde diethyl acetal (6 g.) was added, followed by morpholine (2 drops). After 12 hours the crystals were filtered off, and a further two crops (total yield, 5 g.) obtained from the filtrate by successive dilutions with water. The compound was recrystallised from glacial acetic acid and was identical with the previous preparation (*a*).

2-*Thio*-4-2′-*methylthioethylidenethiazolid*-5-*one* (III; R = CH_2·SMe, R′ = H).—2-Mercaptothiazol-5-one (4 g.) was dissolved in boiling glacial acetic acid (50 c.c.), and methyl 2 : 2-diethoxyethyl sulphide (5·2 g.) was added, followed by piperidine (2 drops). After several hours the condensation product (5·5 g.) separated as pale orange-yellow plates. A small amount (0·2 g.) was obtained on dilution of the mother-liquor with water. The *compound* crystallised from acetic acid in pale yellow plates, m. p. 158° (Found: C, 35·6; H, 3·7; N, 6·8. $C_6H_7ONS_3$ requires C, 35·1; H, 3·4; N, 6·8%).

2-*Thio*-4-n-*butylidenethiazolid*-5-*one*.—2-Mercaptothiazol-5-one (25 g.) was dissolved in boiling glacial acetic acid (250 c.c.), and an excess of *n*-butyraldehyde (40 c.c.) was added, followed by piperidine (2 drops). After 24 hours a crystalline crop (14 g.) was collected, and dilution of the filtrate with water yielded a further crop (10 g.) of the condensation *product* which crystallised as pale yellow needles, m. p. 133°, from acetic acid (Found: C, 44·9; H, 4·8; N, 7·2. $C_7H_9ONS_2$ requires C, 44·9; H, 4·8; N, 7·4%).

2-*Thio*-4-iso*butylidenethiazolid*-5-*one*.—This was prepared similarly from 2-mercaptothiazol-5-one (1 g.), glacial acetic acid (10 c.c.), an excess of *iso*butyraldehyde (2 g.), and piperidine (1 drop). After being kept for 12 hours the solution was filtered from a trace of dark crystalline deposit, and the filtrate diluted with water to give pale brown plates (1·3 g.), m. p. 122°. The 2-*mercapto*-4-iso-*butylidenethiazol*-5-*one* was recrystallised from aqueous acetic acid without further elevation of m. p. (Found: C, 44·8; H, 5·1; S, 34·4%).

2-*Thio*-4-iso*propylidenethiazolid*-5-*one*.—(*a*) 2-Mercaptothiazol-5-one (10 g.) was dissolved in boiling glacial acetic acid, and the solution cooled to 50°. Dry acetone (20 c.c.) was added, a small precipitate filtered off, and the filtrate set aside for 12 hours at room temperature and then diluted with water, whereupon the *iso*propylidene compound was obtained (3 g.).

(*b*) 2-Mercaptothiazol-5-one (5 g.) was dissolved in warm dry acetone (100 c.c.), and morpholine (1 drop) added. The solution was treated with morpholine (1 drop) each day for 6 days, after which the solution contained no unchanged 2-mercaptothiazol-5-one (the thiazole in dilute aqueous sodium hydrogen carbonate, when treated with aqueous iodine–potassium iodide gives a deep purple colour). The solution was diluted with water, giving pale yellow needles, m. p. 211° (4·5 g., 77%), of the condensation product (Found: C, 41·5; H, 4·4; N, 8·0. Calc. for $C_6H_7ONS_2$ C, 41·6; H, 4·1; N, 8·1%). This compound had previously been prepared in 20% yield (Cook, Heilbron, and Levy, *loc. cit.*) by condensing the 2-mercaptothiazol-5-one with acetone in the presence of hydrogen chloride.

2-*Thio*-4-*benzylidenethiazolid*-5-*one*.—2-Mercaptothiazol-5-one (20 g.) was dissolved in boiling glacial acetic acid (200 c.c.), benzaldehyde (21 g.) was added, and the solution treated with piperidine (3 drops). After 15 minutes at room temperature the solution set to a solid mass of yellow crystals. After 12 hours, the crystals were filtered off and a second crop was obtained by concentration of the mother-liquor. A combined crop (31 g., 98%) of the condensation product, m. p. 212—214°, was obtained and no elevation of m. p. was observed on recrystallisation from glacial acetic acid. When melted in admixture with an authentic specimen of 2-thio-4-benzylidenethiazolid-5-one (Cook, Heilbron, and Levy *loc. cit.*) no depression was observed. The condensation was successfully repeated, with theoretical yield, when the piperidine was replaced by primary, secondary, or tertiary bases in catalytic amounts. Thus, aniline, methylaniline, morpholine, diethylamine, dimethylamine, triethylamine, and pyridine were found to be equally effective in the condensation. A small amount of anhydrous sodium acetate was also found to be effective in this condensation.

2-*Thio*-4-p-*hydroxybenzylidenethiazolid*-5-*one*.—2-Mercaptothiazol-5-one (10 g.) was dissolved in boiling glacial acetic acid (100 c.c.), and *p*-hydroxybenzaldehyde (11 g.) was added, followed by piperidine (3 drops). After 12 hours, the crystals were filtered off, and the product was recrystallised from glacial acetic acid in yellow needles, m. p. 199—200° (Found: C, 50·8; H, 3·2. $C_{10}H_7O_2NS_2$ requires C, 50·6; H, 3·0%). Prolonged boiling of the above compound with glacial acetic acid converted it into its geometric isomer, obtained as orange-red needles, m. p. 219—221°. This latter form could also be prepared by dissolving 2-mercaptothiazol-5-one (10 g.) and *p*-hydroxybenzaldehyde (11 g.) in glacial acetic acid (100 c.c.) and saturating the solution with gaseous hydrogen chloride at 0°. On recrystallisation from boiling glacial acetic acid, orange-red needles (6 g.), m. p. 219—221°, were obtained (Found: C, 50·4; H, 3·1; N, 5·8. $C_{10}H_7O_2NS_2$ requires C, 50·6; H, 3·0; N, 5·9%).

2-*Thio*-4-o-*hydroxybenzylidenethiazolid*-5-*one*.—2-Mercaptothiazol-5-one (5 g.) was dissolved in boiling glacial acetic acid (50 c.c.) and *o*-hydroxybenzaldehyde (5 g.) added, followed by piperidine (2 drops). The yellow crystals were filtered off and further crops were obtained by diluting the mother-liquor with water. The product (7·2 g.) was recrystallised from aqueous acid in orange-yellow needles, m. p. 164° (Found: C, 50·4; H, 3·1; N, 5·8. $C_{10}H_7O_2NS_2$ requires C, 50·6; H, 3·0; N, 5·9%).

Reduction of 2-*Thio*-4-*benzylidenethiazolid*-5-*one*.—(*a*) This compound (25 g.) was dissolved in glacial

acetic acid (1 l.), and concentrated hydrochloric acid (0·5 c.c.) was added. Zinc dust (40 g.) was added in 10-g. portions. After 0·5 hour the solution was decolorised and was filtered from the excess of zinc dust. The filtrate was evaporated to dryness *in vacuo*, and the *2-thio-4-benzylthiazolid-5-one* was obtained as a pale yellow crust. The solid was digested with aqueous hydrochloric acid (1 : 1) and filtered, the filtrate containing the last traces of zinc being rejected. The residue (23·5 g.), m. p. 152—153°, was purified by rapid dissolution in cold 2N-sodium hydroxide, followed by acidification and cooling, whereupon pale-yellow to almost colourless matted needles of the benzylthiazol-5-one, m. p. 157—160°, separated. The material could be recrystallised only with great loss, by slow separation from benzene–light petroleum. A portion recrystallised in this manner gave the pure *compound* in almost colourless needles, m. p. 159—160° (Found: C, 53·5; H, 4·1; N, 6·1. $C_{10}H_9ONS_2$ requires C, 53·8; H, 4·1; N, 6·3%).

(*b*) 2-Thio-4-benzylidenethiazolid-5-one (10 g.) was dissolved in warm dioxan (25 c.c.), and zinc dust (15 g.) was added. Glacial acetic acid (10 c.c.) was added and the solution gently heated until the yellow colour was discharged. The excess of zinc dust was filtered off and the filtrate on dilution with water and cooling to 0° slowly deposited 2-mercapto-4-benzylthiazol-5-one as a micro-crystalline powder (7·5 g.), m. p. 157—160°, recrystallised as described in the previous experiment.

The above compound (1·8 g.) was triturated with morpholine (1·69 g.) dissolved in dry acetone (4 c.c.). An exothermic reaction was observed, followed by sudden crystallisation. The product (3·2 g.) was filtered off and a portion (0·5 g.) was added to hot acetone (5 c.c.) and dissolved by the addition of water (3 drops). On cooling, rectangular plates of the *morpholinium* salt of *N*-dithiocarboxy-β-phenylalanine morpholide, m. p. 150°, were obtained (Found: C, 54·3; H, 6·6; N, 10·6; S, 16·3. $C_{18}H_{27}O_3N_3S_2$ requires C, 54·4; H, 6·8; N, 10·6; S, 15·9%). This salt (0·5 g.) when treated with 2N-hydrochloric acid was reconverted into 2-mercapto-4-benzylthiazol-5-one, m. p. 159—160°, undepressed when melted in admixture with the previously prepared compound.

The above benzylthiazol-5-one (5 g.) was suspended in methanol (20 c.c.), and a solution of sodium (1·2 g.) in methanol (20 c.c.) was run in, whereupon the compound dissolved completely. The solution was kept at room temperature for 10 minutes, and the excess of alkali removed by adding to it a small excess of 5N-methanolic hydrogen chloride (using phenolphthalein as indicator). Sodium chloride was filtered off and the filtrate evaporated to dryness. The residual oil, when rubbed with ether, set to a crystalline mass. The crystals were dissolved in chloroform, the solution treated with charcoal. The filtrate on dilution with ether, followed by cooling, deposited β-phenylalanine methyl ester hydrochloride as colourless needles (2·5 g.), m. p. 156—158°, undepressed on admixture with the authentic compound.

Preparation of 2-Thio-4-benzylthiazolid-5-one from β-Phenylalanine.—β-Phenylalanine (5 g.) was esterified by suspending it in methanol (25 c.c.) and heating the mixture under reflux with a current of gaseous hydrogen chloride passing through it for 0·5 hour. The solution was then evaporated to dryness *in vacuo*, and the β-phenylalanine methyl ester hydrochloride (5·6 g.), m. p. 154—155°, obtained as colourless needles was used without further purification. The ester hydrochloride (5 g.) was dissolved in chloroform (100 c.c.) and was titrated against 20% aqueous sodium hydroxide (phenolphthalein). The chloroform layer was separated and the aqueous solution extracted twice with chloroform (25-c.c. portions). The chloroform extracts were dried ($MgSO_4$), the solvent was distilled off *in vacuo*, and the residual oil (2 g.) was kept with liquid ammonia (100 c.c.) in a sealed vessel for 30 hours. On evaporation of the ammonia, a white crystalline residue was obtained which was dissolved in hot chloroform and filtered from a little residual solid. The filtrate, diluted with light petroleum, gave colourless prisms of β-phenylalanine amide (85%), m. p. 139—140°. The above amide (0·5 g.) was dissolved in a minimum of ethanol at room temperature with just sufficient water to give a clear solution, and an excess of carbon disulphide (1 g.) was added. The clear solution was set aside for 0·5 hour at room temperature and then acidified with concentrated hydrochloric acid (10 c.c.), and the excess of carbon disulphide removed *in vacuo*. On dilution with water (10 c.c.) and cooling in ice 2-mercapto-4-benzylthiazol-5-one separated in colourless needles, m. p. 159—160°, undepressed on admixture with the compound prepared by the reduction of 2-mercapto-5-benzylidenethiazol-5-one (Found: C, 53·5; H, 4·1; N, 6·1. Calc. for $C_{10}H_9ONS_2$: C, 53·6; H, 4·1; N, 6·3%).

5-Imino-4-phenyl-2 : 2-dimethyloxazolidine.—α-Aminobenzyl cyanide (20 g.) was dissolved in cold acetone (300 c.c.), and sodium methoxide obtained from sodium (0·8 g.) in methanol (5 c.c.) was added. After some time, an exothermic reaction was observed, and the mixture was cooled in ice and kept overnight at 0°. The *oxazolidine* (23 g.) which separated was recrystallised from dry acetone in colourless needles, m. p. 142—144° (Found: C, 69·9; H, 7·4; N, 15·2. $C_{11}H_{14}ON_2$ requires C, 69·5; H, 7·4; N, 14·7%).

The above oxazolidine (15 g.) was heated under reflux with water (40 c.c.). On cooling, the solution set to a solid mass of crystals, which were filtered off, and the α-aminophenylacetamide (13 g.) was recrystallised from water; m. p. 132—133°.

The above amide (20 g.) was dissolved in hot dry ethanol (50 c.c.), and an excess of carbon disulphide (40 c.c.) was added. The solution was kept at room temperature for 1 hour and finally boiled under reflux for 15 minutes. The excess of carbon disulphide was removed *in vacuo*, and the solution poured on crushed ice and hydrochloric acid. The crystalline precipitate so obtained was filtered off after 1 hour at 0°. On recrystallisation from aqueous ethanol containing a trace of dilute aqueous hydrochloric acid, 2-mercapto-4-phenylthiazol-5-one (12 g.) was obtained in pale yellow prismatic needles, m. p. 155—156° (decomp.) (Found: C, 51·8; H, 3·5; N, 6·9; S, 30·2. $C_9H_7ONS_2$ requires C, 51·7; H, 3·4; N, 6·7; S, 30·7%).

The above phenylthiazol-5-one was triturated with acetone (5 c.c.) containing morpholine (1·90 g.). The compound immediately dissolved, giving a yellow solution which soon became dark. After some minutes the colour again rapidly faded and the crystalline deposit of the morpholinium salt (4·4 g.) was obtained. The *morpholinium* salt of *N*-dithiocarboxyphenylglycine morpholide (cf. VI) was recrystallised from dry acetone (as described for the previous morpholinium salt) in colourless prisms, m. p. 140—141° (Found: C, 53·6; H, 6·5; N, 11·0; S, 16·4. $C_{17}H_{25}O_3N_3S_2$ requires C, 53·3; H, 6·6; N, 11·0; S, 16·7%).

The above morpholinium salt (0·5 g.), dissolved in a little water, was treated with 15% hydrochloric acid, whereupon a precipitate was obtained which, after recrystallisation from aqueous ethanol containing a few drops of hydrochloric acid, was identified with the previously prepared 2-mercapto-4-phenylthiazol-5-one, m. p. and mixed m. p. 155—156°.

Reduction of 2-*Thio*-4-p-*hydroxybenzylidenethiazolid*-5-*one*.—This compound (5 g.) was dissolved in glacial acetic acid (150 c.c.) and reduced in the usual manner with zinc dust (7 g.). After removal of the excess of zinc dust, the filtrate on cooling deposited some crystals of zinc acetate which were filtered off and rejected. The filtrate was diluted with light petroleum (b.p. 60—80°) and kept at 0°, whereupon colourless needles (1 g.) slowly crystallised. The 2-*thio*-4-p-*hydroxybenzylthiazolid*-5-*one* recrystallised from glacial acetic acid–light petroleum in colourless needles, m. p. 162—164° (Found: C, 49·8; H, 4·0; N, 6·0; S, 26·2. $C_{10}H_9O_3NS_2$ requires C, 50·2; H, 3·8; N, 5·9; S, 26·8%).

The filtrate was evaporated to dryness, and the residual tar subjected to chromatography in ethyl acetate on an alumina column. The main fraction of the eluent, when diluted with light petroleum, deposited a further crop of crystals (1·5 g.) which were recrystallised in the above manner.

Reduction of 2-*Thio*-4-cyclo*hexylidenethiazolid*-5-*one*.—The compound (2 g.) was dissolved in acetic acid (25 c.c.) and reduced as described in the previous experiment with zinc dust (5 g.). 2-*Thio*-4-cyclo*hexylthiazolid*-5-*one* (0·25 g.) separated from aqueous acetic acid in pale yellow needles, m. p. 185—186° (Found: N, 6·1; S, 29·8. $C_9H_{13}ONS_2$ requires N, 6·5; S, 29·8%).

Reduction of 2-*Thio*-4-*methylthioethylidenethiazolid*-5-*one*.—(*a*) The compound (3 g.), dissolved in acetic acid (15 c.c.), was reduced in the usual manner with zinc dust (4 g.). Methanethiol was evolved and, after removing the solvent *in vacuo*, the residual gum was sublimed in a high vacuum at 85—90°, whereafter pale yellow plates (0·5 g.) were collected. 2-*Thio*-4-*ethylthiazolid*-5-*one* (0·5 g.) was recrystallised from ether after a second sublimation and then had m. p. 79—80° (Found: C, 38·15; H, 4·75; N, 8·7. $C_5H_7ONS_2$ requires C, 37·3; H, 4·55; N, 8·7%).

(*b*) The above reduced compound (0·2 g.) was dissolved in ethanol (2 c.c.), and 5N-ethanolic hydrogen chloride (5 c.c.) added. The solution was boiled under reflux for 10 minutes, the solvent evaporated *in vacuo*, and the residual oil crystallised by rubbing with ether. Recrystallisation from ethanol–ether yielded silky colourless needles of ethyl (±)-α-aminobutyrate hydrochloride, m. p. 129—131° (lit., m. p. 130—131°) (Found: N, 7·8. $C_6H_{13}O_2N$,HCl requires N, 8·3%).

Preparation of α-*Amino*-n-*butyric Acid from* 2-*Thio*-4-*ethylidenethiazolid*-5-*one*.—The thiothiazolidone (4 g.) was dissolved in boiling acetic acid (30 c.c.), and red phosphorus (6 g.) added, followed by 40% aqueous hydrogen iodide (12 c.c.). The mixture was then boiled under reflux for 4 hours. The solution was filtered and the filtrate diluted with a little water. A trace of unchanged material was rejected and the filtrate evaporated to dryness *in vacuo*. The residual oil was dissolved in aqueous ethanol (25 c.c.) and filtered through charcoal. The filtrate was cooled to 0°, and pyridine (5 c.c.) added. After the mixture had been kept overnight at 0° the microcrystalline amino-acid (2 g.) was filtered off and sublimed at 170° in a high vacuum. α-*Amino*-n-*butyric acid* recrystallised from aqueous ethanol in small colourless plates, m. p. 300° (Found: C, 46·6; H, 8·6; N, 13·55. $C_4H_9O_2N$ requires C, 46·6; H, 8·7; N, 13·6%).

The above acid was esterified with ethanolic hydrogen chloride and ethyl α-amino-*n*-butyrate hydrochloride crystallised from ethanol in colourless needles, m. p. 129—30°, undepressed on admixture with the ester hydrochloride previously obtained by the degradation of 2-mercapto-4-ethylthiazol-5-one.

β-*Phenylalanine*.—2-Thio-4-benzylidenethiazolid-5-one (3 g.) was suspended in glacial acetic acid (20 c.c.), and red phosphorus (4 g.) added, followed by 40% aqueous hydrogen iodide (10 c.c.). The whole was then heated under reflux for 1·5 hours. The solution was filtered and the filtrate diluted with water. A trace of gummy material was rejected, the filtrate evaporated to dryness *in vacuo*, and the residue dissolved in hot water (20 c.c.) and filtered through charcoal. The filtrate was concentrated to 15 c.c., and pyridine (10 c.c.) added. After 12 hours at 0° the silky plates deposited were recrystallised from aqueous ethanol, β-phenyl-α-alanine (70%) being obtained in large colourless plates, m. p. 282—284° (decomp.). The amino-acid was converted by methanolic hydrogen chloride into β-phenylalanine methyl ester hydrochloride, m. p. 156—158°, undepressed on admixture with an authentic specimen.

(±)-*Tyrosine*.—Thio-4-*p*-hydroxybenzylidenethiazolid-5-one (3 g.), suspended in glacial acetic acid, was similarly subjected to reductive hydrolysis with red phosphorus (4 g.) and 40% aqueous hydrogen iodide (10 g.). The (±)-tyrosine was obtained from boiling water as colourless needles (1·7 g.), m. p. 290—295° (sealed tube), and characterised as the ethyl ester hydrochloride which formed colourless needles, m. p. 166°, undepressed on admixture with a specimen prepared from authentic (±)-tyrosine.

(±)-*Valine*.—Thio-4-*iso*propylidenethiazolid-5-one (3 g.), dissolved in hot acetic acid (20 c.c.), was reduced in the above manner with red phosphorus (5 g.) and 40% aqueous hydrogen iodide (10 g.); (±)-valine (1·6 g.) separated from aqueous ethanol in colourless plates, m. p. 298° (sealed tube). The compound was characterised by the preparation of its ethyl ester hydrochloride which formed hygroscopic crystals, m. p. 73—76° (lit., m. p. 76°). The free ester was obtained from the above compound and characterised as its picrate which formed microcrystals (from aqueous ethanol), m. p. 138—139°, undepressed on admixture with an authentic specimen.

(±)-*Norleucine*.—2-Thio-4-*n*-butylidenethiazolid-5-one (5 g.), dissolved in hot acetic acid (25 c.c.), was reduced in the usual manner with red phosphorus (5 g.) and aqueous hydrogen iodide (10 c.c.); (±)-norleucine (2 g.) separated in colourless needles from aqueous ethanol and sublimed without melting, above 300° (Found: C, 54·9; H, 10·1; N, 10·5. Calc. for $C_6H_{13}O_2N$: C, 54·9; H, 10·0; N, 10·7%).

(±)-*Leucine*.—2-Thio-4-*iso*butylidenethiazolid-5-one (2·4 g.) in hot acetic acid (20 c.c.) was also reduced in the above manner, whereupon (±)-leucine (1·3 g.) separated from hot water in thin lustrous plates, m. p. 293—295° (sealed tube). The amino-acid (0·25 g.) in aqueous 2N-sodium hydroxide (5 c.c.) was treated with 3 : 5-dinitrobenzoyl chloride (0·3 g.). After being shaken for 10 minutes, the solution was acidified and the precipitated (±)-3 : 5-dinitrobenzoyl-leucine separated from aqueous ethanol in pale yellow needles, m. p. 187—189° (Found: N, 13·05. Calc. for $C_{13}H_{15}O_7N_3$: N, 12·9%).

(±)-*Methionine*.—2-Thio-4-methylthioethylidenethiazolid-5-one (2 g.) in acetic acid (25 c.c.) was

heated under reflux with red phosphorus (4 g.) and 40% aqueous hydrogen iodide for 30 minutes. Some methanethiol was evolved. The solution was filtered and the filtrate evaporated to dryness *in vacuo*. The residual oil was dissolved in water (10 c.c.), and the unchanged material rejected. The filtrate was again concentrated to dryness *in vacuo*, and the residue dissolved in aqueous ethanol (15 c.c.), treated with charcoal and cooled to 0°, and pyridine (5 c.c.) was added. After some hours the (±)-methionine (0·3 g.) was collected and recrystallised from aqueous ethanol in colourless needles, m. p. 275—280° (sealed tube), undepressed by admixture with authentic (±)-methionine.

The above acid, dissolved in aqueous sodium hydroxide, was benzoylated to give (±)-*N*-benzoylmethionine, crystallising from aqueous ethanol in colourless needles, m. p. 143—144°, undepressed by admixture with the compound prepared from authentic (±)-methionine.

(±)-cyclo*Hexylglycine*.—2-Thio-4-*cyclo*hexylidenethiazolid-5-one (2·2 g.) was similarly converted into (±)-*cyclo*hexylglycine (1·3 g.). The amino-acid was almost insoluble in hot water and was conveniently crystallised from hot acetic acid in colourless needles, m. p. 296—297°. The picrate separated from acetic acid in small crystals, m. p. 186—187° (cf. Zelinsky and Studnikoff, Ber., 1906, **39**, 1723).

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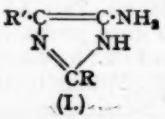
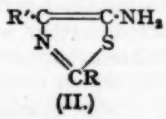
493. *Studies in the Azole Series. Part XX. Some Novel Syntheses of Purines and Thiazolopyrimidines.*

By A. H. COOK and E. SMITH.

The ready cyclisation, by various procedures, of certain 5-aminoglyoxaline- and 5-aminothiazole-4-carboxyamides to the corresponding purines and thiazolopyrimidines is described.

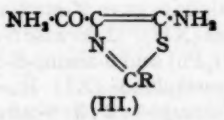
EARLIER in this series (Parts XII—XIV, this vol., pp. 1064—1074) the synthesis of 5-amino-4-carbethoxy-glyoxalines (I) and -thiazoles (II; R′ = CO_2Et) and their conversion into purines and thiazolopyrimidines, respectively, was described. This approach to the purine ring system


(I.)


(II.)

appeared capable of extension to the 4-carboxyamides and 4-cyanides. Such amides have been described (Cook, Heilbron, and Smith, Part XVII, this vol., p. 1440) and thus presented a convenient alternative approach to the system under discussion.

A purine synthesis of the type here envisaged has been effected by Sarasin and Wegmann (*Helv. Chim. Acta*, 1924, **7**, 713) who obtained 7-methylxanthine by treating 5-amino-3-methylglyoxaline-4-carboxyamide with ethyl carbonate. This reaction was improved (Mann and Porter, *J.*, 1945, 752) by employing ethyl chloroformate but still required a high temperature and the presence of potassium carbonate. With the possibility in mind of using this type of approach for the synthesis of sensitive purines, a milder cyclisation procedure was accordingly sought. Modification of the alcohol residue in ethyl chloroformate by employing the thiophenyl instead of the ethoxyl group gave the desired type of reactivity, *i.e.*, ease of reaction with amines and formation of products from which subsequent smooth removal of the ester residue proved feasible. Thus, treatment of 5-amino-2-methylthiothiazole-4-carboxyamide (III; R = SMe) (cf. Part XVII, *loc. cit.*) with phenyl chlorothiolformate, Ph·S·CO·Cl (Rivière, *Bull. Soc. chim.*,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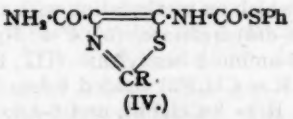
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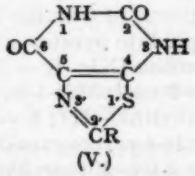
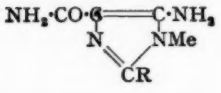

(V.)

1901, **1**, 733) at room temperature yielded 5-(*phenylthioformamido*)-2-*methylthiothiazole*-4-*carboxyamide* (IV; R = SMe). This compound on being heated above its melting point readily lost thiophenol, and the same result was obtained when it was boiled in pyridine for 10 minutes, with consequent production of 2 : 6-*diketo*-2′-*methylthio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)-*pyrimidine* (V; R = SMe). This ready cyclisation was extended in a similar fashion to 5-*amino*-

2-*benzylthiothiazole*-4-*carboxyamide* and 5-amino-2-benzylthiazole-4-carboxyamide which were converted, respectively, into 5-(*phenylthioformamido*)-2-*benzylthio*- (IV; R = S·CH_2Ph) and 5-*phenylthioformamido*)-2-*benzyl*-*thiazole*-4-*carboxyamide* (IV; R = CH_2Ph), with subsequent cyclisation to 2 : 6-*diketo*-2′-*benzylthio*- (V; R = S·CH_2Ph) and to 2 : 6-*diketo*-2′-*benzyl*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (V; R = CH_2Ph). This route was also used for the conversion of 5-*amino*-2-*methylthio*-1-*methylglyoxaline*-4-*carboxyamide* (VI; R = SMe) through 5-(*phenylthioformamido*)-2-*methylthio*-1-*methylglyoxaline*-4-*carboxyamide* (VII) into 2 : 6-*dihydroxy*-8-*methylthio*-9-*methylpurine* (VIII). This method could doubtless be extended to the synthesis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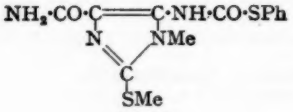
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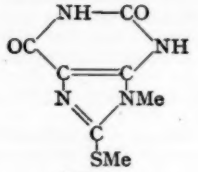
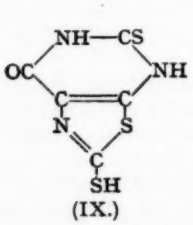
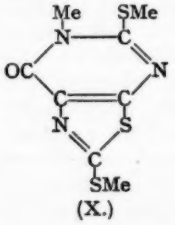
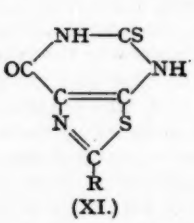

(VIII.)

of purines and thiazolopyrimidines with a mercapto-group in the 2-position by employing phenyl chlorodithioformate, but another approach to compounds of this type soon presented itself.

It has been shown that α-amino-nitriles react with carbon disulphide in non-basic solvents to give 5-amino-2-mercaptothiazoles (Cook, Heilbron, and Levy, Part II, *J.*, 1947, 1598). It was observed that on treatment of aminocyanoacetamide with carbon disulphide in pyridine a product was obtained which was not 5-amino-2-mercaptothiazole-4-carboxyamide or an isomeride thereof. Analyses of the new product showed that it was derived from aminocyanoacetamide (1 mol.) and carbon disulphide (2 mols.) with loss of hydrogen sulphide (1 mol.), and it was further shown that treatment with methyl sulphate converted it into a trimethyl derivative. It appeared likely that aminocyanoacetamide had reacted with carbon disulphide to give initially 5-amino-2-mercaptothiazole-4-carboxyamide (III; R = SH) (cf. Part XVII, *loc. cit.*) and that the latter had reacted further with carbon disulphide to give, probably through the intermediation of a dithiocarbamate, 2′-*mercapto*-6-*keto*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (IX) which on methylation gave 6-keto-2 : 2′-dimethylthio-1-methyl-1 : 6-dihydrothiazolo(5′ : 4′-4 : 5)pyrimidine (X). Indeed, 5-amino-2-mercaptothiazole-4-carboxyamide


(IX.)


(X.)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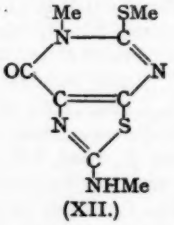

(XII.)

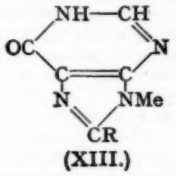
itself gave the compound (IX) when boiled under reflux with carbon disulphide in pyridine. The trimethyl derivative of this, viz. compound (X), proved in fact to be identical with the product already assigned the same structure and earlier synthesised in these laboratories by a different route (Part XII, *loc. cit.*, 1064).

This type of cyclisation was found to be applicable to other 5-aminoazole-4-carboxyamides. Treatment of 5-amino-2-methylaminothiazole-4-carboxyamide (III; R = NHMe) with carbon disulphide in pyridine gave 2′-*methylamino*-6-*keto*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)-*pyrimidine* (XI; R = NHMe) which on methylation with methyl sulphate gave 2′-*methylamino*-6-*keto*-2-*methylthio*-1-*methyl*-1 : 6-*dihydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XII). Likewise 5-amino-2-methylthio- (III; R = SMe), 5-amino-2-benzylthio- (III; R = S·CH_2Ph) and 5-amino-2-benzylthiazole-4-carboxyamide (III; R = CH_2Ph) yielded 6-*keto* 2-*thio*-2′-*methylthio*- (XI; R = SMe), 6-*keto* 2-*thio*-2′-*benzylthio*- (XI; R = S·CH_2Ph), and 6-*keto* 2-*thio*-2′-*benzyl*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XI; R = CH_2Ph), respectively. In a similar manner, treatment of 5-amino-2-mercapto-1-methylglyoxaline-4-carboxyamide and 5-amino-1-methylglyoxaline-4-carboxyamide with carbon disulphide yielded the corresponding purines, 6-*hydroxy*-2 : 8-*dimercapto*-9-*methyluric acid* and 6-*hydroxy*-2-*mercapto*-9-*methylpurine*, respectively.

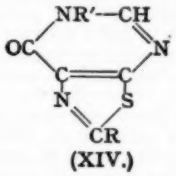
An approach to compounds of the type (XIII) containing the hypoxanthine ring system, by

treating 5-amino-2-methylthio-1-methylglyoxaline-4-carboxyamide (VI; R = SMe) and 5-amino-1-methylglyoxaline-4-carboxyamide (VI; R = H) with formic acid led to 6-*hydroxy*-8-*methylthio*-9-*methylpurine* (XIII; R = SMe) and to 6-hydroxy-9-methylpurine (9-methylhypoxanthine) (XIII; R = H), respectively, of which products the latter had been described earlier (Fischer, *Ber.*, 1898, **31**, 114).

The attempted synthesis of compounds of the type (XIV) by interaction of 5-amino-2-methylthiothiazole-4-carboxyamide (III; R = SMe) with formic acid, however, yielded only the corresponding *N*-formyl derivative. The latter, however, was converted by acetic anhydride,



(XIII.)



(XIV.)

with elimination of water, into 6-*keto*-2′-*methylthio*-1 : 6-*dihydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XIV; R = SMe, R′ = H) which was also obtained in one stage by treating the thiazole (III; R = SMe) with ethyl orthoformate. Compound (XIV; R = SMe, R′ = H) with methyl sulphate and alkali yielded a monomethyl derivative, which was formulated as 6-*kelo*-2′-*methylthio*-1-*methyl*-1 : 6-*dihydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XIV; R = SMe, R′ = Me). Similar reactions were effected with 5-amino-2-benzylthiothiazole-4-carboxyamide (III; R = S·CH_2Ph) and 5-amino-2-benzylthiazole-4-carboxyamide (III; R = CH_2Ph) to give respectively, 6-*keto*-2′-*benzylthio*- (XIV; R = S·CH_2Ph) and to 6-*keto*-2′-*benzyl*-1 : 6-*dihydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XIV) (R = CH_2Ph). It may be noted that attempted cyclisation of this type of compound carrying a reactive functional group in the 2-position (*e.g.*, R = SH, NHMe, or NHPh) led only to acetyl or ethoxymethylene derivatives and not to bicyclic products.

Experimental.

2 : 6-*Diketo*-2′-*methylthio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (V; R = SMe).—5-Amino-2-methylthiothiazole-4-carboxyamide (2·5 g.) was dissolved in anhydrous dioxan (30 c.c.) and to the solution was added phenyl chlorothiolformate (1·3 g.). The solution was set aside for several hours at room temperature and then cooled to 0° for 1 hour, whereupon crystals of the hydrochloride, m. p. 195°, slowly separated. These (0·9 g.) were filtered off; the filtrate was evaporated to dryness *in vacuo*, and the residue was extracted with hot benzene (40 c.c.). This extract was evaporated to small bulk (*ca.* 5 c.c.), crystals (1·8 g.) of 5-(*phenylthioformamido*)-2-*methylthiothiazole*-4-*carboxyamide* (IV; R = SMe) separating. The product crystallised from benzene in colourless felted needles, m. p. 175° (decomp.) and 300° (Found: C, 44·6; H, 3·3; N, 13·0. $C_{13}H_{11}O_2N_3S_3$ requires C, 44·3; H, 3·4; N, 12·9%).

The above compound (2·4 g.) was dissolved in dry pyridine (5 c.c.). When this solution was boiled under reflux for 10 minutes, thiophenol was copiously evolved. The solution was cooled and acidified with 6N-hydrochloric acid (15 c.c.) and then set aside at 0°. The product, 2 : 6-*diketo*-2′-*methylthio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (1·5 g.), was filtered off and crystallised from glacial acetic acid in colourless small prisms, m. p. 295—300° (Found: C, 33·5; H, 2·3; N, 19·4. $C_6H_5O_2N_3S_2$ requires C, 33·5; H, 2·3; N, 19·5%).

2 : 6-*Diketo*-2′-*benzylthio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (V; R = S·CH_2Ph).—5-Amino-2-mercaptothiazole-4-carboxyamide (2·0 g.) was dissolved in N-sodium hydroxide (20 c.c.) and shaken for 1 hour at room temp. with excess of benzyl chloride (4 g.). The product which separated, 5-*amino*-2-*benzylthiothiazole*-4-*carboxyamide* (III; R = S·CH_2Ph) (2·4 g.), was filtered off and recrystallised from benzene, forming colourless felted needles, m. p. 143—144° (Found: N, 15·5. $C_{11}H_{11}ON_3S_2$ requires N, 15·8%).

5-Amino-2-benzylthiothiazole-4-carboxyamide (1·0 g.) was dissolved in dry acetone (40 c.c.). Phenyl chlorothiolformate (0·5 g.) was added and the solution set aside at room temperature for 6 hours and then evaporated to dryness *in vacuo*. The residue was extracted with hot benzene and filtered. Evaporation of the filtrate to a small bulk (*ca.* 5 c.c.) yielded crystals (0·6 g.) of 5-(*phenylthioformamido*)-2-*benzylthiothiazole*-4-*carboxyamide* (IV; R = S·CH_2Ph), m. p. 143°, which crystallised from benzene–light petroleum in colourless rods (Found: C, 54·0; H, 3·8; N, 10·65. $C_{18}H_{15}O_2N_3S_3$ requires C, 53·9; H, 3·8; H, 10·5%).

The above compound (0·5 g.) was dissolved in dry pyridine (2 c.c.) and the solution was boiled under reflux for 10 minutes and then evaporated to dryness *in vacuo*. The residue of 2 : 6-*diketo*-2′-*benzylthio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (0·3 g.) was collected. It crystallised from glacial acetic acid in colourless small prisms, m. p. 290—295° (Found: C, 49·4; H, 3·0; N, 14·7. $C_{13}H_9O_2N_3S_2$ requires C, 49·5; H, 3·1; N, 14·4%).

2 : 6-*Diketo*-2′-*benzyl*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (V; R = CH_2Ph). 5-Amino-2-benzylthiazole-4-carboxyamide (1·0 g.) was dissolved in anhydrous dioxan (30 c.c.) and phenyl chlorothiolformate (1·0 g.) was added. After being kept at room temperature for 6 hours the solution was cooled to 0°, whereupon crystals of the hydrochloride (0·3 g.), m. p. 215°, separated The

solution was evaporated to dryness *in vacuo* and the residue extracted with hot benzene and filtered. Evaporation of this extract to small bulk yielded crystals (0·7 g.) of 5-(*phenylthioformamido*)-2-*benzylthiazole*-4-*carboxyamide* (IV; R = CH_2Ph), m. p. 148°. This crystallised from benzene–light petroleum in felted needles (Found: N, 11·2. $C_{18}H_{15}O_2N_3S_2$ requires N, 11·4%).

The above compound (0·5 g.) was dissolved in dry pyridine and the solution was boiled under reflux for 10 minutes. The solvent was then removed *in vacuo*. The residue (0·3 g.) of 2 : 6-*diketo*-2′-*benzyl*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* crystallised from glacial acetic acid–ether in boat-shaped small prisms, m. p. 295—300° (Found: C, 55·7; H, 3·7; N, 16·2%. $C_{13}H_9O_2N_3S$ requires C, 55·6; H, 3·5; N, 16·2%).

2 : 6-*Dihydroxy*-8-*methylthio*-9-*methylpurine* (VIII).—5-Amino-2-mercapto-1-methylglyoxaline-4-carboxyamide (1·6 g.), dissolved in N-sodium hydroxide (5 c.c.), was shaken for 30 minutes at 0° with excess of methyl sulphate. The product which separated, 5-*amino*-2-*methylthio*-1-*methylglyoxaline*-4-*carboxyamide* (VI; R = SMe) (1·1 g.) was filtered off, washed with water and then with ether. It crystallised from benzene in colourless platelets, m. p. 176° (Found: N, 29·9. $C_6H_{10}ON_4S$ requires N, 30·1%). 5-Amino-2-methylthio-1-methylglyoxaline-4-carboxyamide (VI) (1·4 g.) was dissolved in dry acetone (100 c.c.). Phenyl chlorothiolformate (0·8 g.) was added. When the mixture was kept at room temperature for 30 minutes crystals (0·7 g.) of the *hydrochloride* separated. These were filtered off and crystallised from ethanol in colourless prisms, m. p. 217—218° (Found: C, 33·0; H, 5·3. $C_6H_{11}ON_4SCl$ requires C, 32·6; H, 5·0%). The filtrate was evaporated to dryness under diminished pressure and the residue recrystallised from *iso*butanol in colourless prisms of 5-(*phenylthioformamido*)-1-*methyl*-2-*methylthioglyoxaline*-4-*carboxyamide* (VII) which decomposed gradually up to 300° (Found: N, 17·7. $C_{13}H_{14}O_2N_4S_2$ requires N, 17·4%).

The above compound (0·3 g.) was dissolved in dry pyridine (5 c.c.), and the solution was heated under reflux for 15 minutes and then evaporated to dryness *in vacuo*. The residue of 2 : 6-*dihydroxy*-8-*methylthio*-9-*methylpurine* (0·15 g.) was collected and crystallised from pyridine–ether in colourless small prisms, m. p. 320° (decomp.) (Found: C, 41·1; H, 3·9; N, 25·9. $C_7H_8O_2N_4S$ requires C, 39·6; H, 3·8; N, 26·4%).

2′-*Mercapto*-6-*keto*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (IX).—(a) *From aminocyanoacetamide.* Aminocyanoacetamide (0·3 g.) was dissolved in pyridine (40 c.c.) and boiled under reflux for 3 hours with carbon disulphide (5 c.c.). The solution was cooled, diluted with 2N-hydrochloric acid, and after being kept at 0° was filtered. The product, 6-*hydroxy*-2′-*mercapto*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (0·4 g.), crystallised from (1 : 1) quinoline–acetic acid in brownish small prisms which did not melt below 450°. The product was obtained colourless on dissolution in a large volume of N-sodium hydroxide solution, followed by precipitation with acetic acid (Found: C, 28·1; H, 1·7; N, 18·9. $C_5H_3ON_3S_2$ requires C, 27·7; H, 1·4; N, 19·3%).

(b) *From* 5-*amino*-2-*mercaptothiazole*-4-*carboxyamide.* This amide (0·5 g.) was dissolved in pyridine (40 c.c.) containing carbon disulphide (5 c.c.) and the mixture, after being heated under reflux (3 hours), was treated as in the preceding section.

The above compound (0·2 g.) was dissolved in N-sodium hydroxide solution and shaken for 1 hour with excess (1 c.c.) of methyl sulphate. The solid which separated was washed thoroughly with water and ether. This product, 6-keto-2 : 2′-dimethylthio-1-methyl-1 : 6-dihydrothiazolo(5′ : 4′-4 : 5)-pyrimidine (X), crystallised from ethanol in rosettes of needles, m. p. 222·5°, undepressed by admixture with authentic material (Cook, Heilbron, Macdonald, and Mahadevan, *loc. cit.*) (Found: C, 37·15; H, 3·55; N, 16·05. Calc. for $C_8H_9ON_3S_3$: C, 37·05; H, 3·5; N, 16·2%).

2′-*Methylamino*-6-*keto*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XI; R = NHMe).—5-Amino-2-methylaminothiazole-4-carboxyamide (0·4 g.), dissolved in pyridine (15 c.c.) was heated under reflux for 3 hours with carbon disulphide, a yellow solid being slowly deposited. The solid (0·3 g.) was filtered off and purified by dissolution in 2N-aqueous ammonia, followed by acidification with acetic acid, the *thiazolopyrimidine*, m. p. >300°, separating in small prisms (Found: C, 33·3; H, 2·9. $C_6H_5ON_4S_2$ requires C, 33·6; H, 2·8%).

The above compound (0·1 g.) was dissolved in 2N-sodium hydroxide and shaken for 30 minutes with methyl sulphate (0·5 c.c.). The yellow solid which separated, 2′-*methylamino*-6-*keto*-2-*methylthio*-1-*methyl*-1 : 6-*dihydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XII) was filtered, washed thoroughly with water and ether, and crystallised from (1 : 1) glacial acetic acid–methanol in colourless prisms, m. p. 299—302° (Found: C, 39·5; H, 4·3; N, 23·5. $C_8H_{10}ON_4S_2$ requires C, 39·7; H, 4·2; N, 23·1%).

6-*Keto*-2′-*methylthio*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XI; R = SMe).—5-Amino-2-methylthiothiazole-4-carboxyamide (2·0 g.), dissolved in pyridine (5 c.c.), was heated under reflux for 8 hours with carbon disulphide (2 c.c.). The solvent was removed *in vacuo*, and the residue extracted with N-sodium hydroxide (5 c.c.) at 40°. Filtration and acidification of the extract with 2N-hydrochloric acid yielded a precipitate (0·1 g.) of the *thiazolopyrimidine*, which was purified by dissolution in N-sodium hydroxide, followed by precipitation with N-hydrochloric acid, giving small yellow prisms, m. p. 270—275° (Found: C, 31·0; H, 2·3. $C_6H_5ON_3S_3$ requires C, 31·1; H, 2·2%).

6-*Keto*-2′-*benzylthio*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XI; R = S·CH_2Ph).—5-Amino-2-benzylthiothiazole-4-carboxyamide (2·0 g.), dissolved in pyridine (10 c.c.), was heated under reflux for 8 hours with carbon disulphide (2 c.c.). The solution was worked up as in the foregoing preparation to yield the thiazolopyrimidine (0·1 g.) as yellow small prisms which were purified by dissolution in alkali, followed by precipitation with acid, giving an almost white *product*, m. p. 275—280° (Found: C, 46·8; H, 3·0. $C_{12}H_9ON_3S_3$ requires C, 46·9; H, 3·0%).

6-*Keto*-2-*thio*-2′-*benzyl*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XI; R = CH_2Ph).—5-Amino-2-benzylthiazole-4-carboxyamide (1·5 g.) in pyridine (20 c.c.) was heated under reflux for 8 hours with carbon disulphide (4 c.c.), and the solution worked up as in earlier examples, to give the *thiazolopyrimidine* (0·3 g.) which crystallised from glacial acetic acid in colourless small prisms, m. p. 280° (Found: C, 52·1; H, 3·2; N, 15·0. $C_{12}H_9ON_3S_2$ requires C, 52·35; H, 3·3; N, 15·25%).

6-*Hydroxy*-2 : 8-*dimercapto*-9-*methyluric Acid.*—5-Amino-2-mercapto-1-methylglyoxaline-4-carboxyamide (0·1 g.), dissolved in boiling pyridine (10 c.c.), was heated under reflux for 12 hours with carbon

disulphide (2 c.c.). The solution was cooled and diluted with 2N-hydrochloric acid (35 c.c.), thereby precipitating the *purine* (0·05 g.). This material had m. p. >300° and was purified by repeated dissolution in hot pyridine, followed by precipitation with 2N-hydrochloric acid (Found: C, 34·2; H, 3·1; N, 25·9. $C_6H_6ON_4S_2$ requires C, 33·6; H, 2·8; N, 26·1%).

6-Hydroxy-2-mercapto-9-methylpurine.—5-Amino-1-methylglyoxaline-4-carboxyamide (0·1 g.), dissolved in boiling pyridine (25 c.c.), was heated under reflux for 12 hours with carbon disulphide (2 c.c.), the purine gradually separating from the hot solution. This (0·06 g.) was filtered off, purified by dissolution in 2N-sodium hydroxide and precipitation with 2N-hydrochloric acid; it then crystallised from water in small colourless prisms of the *purine hemihydrate*, m. p. 315° (Found: C, 38·1; H, 3·8; N, 29·3. $C_6H_6ON_4S,\frac{1}{2}H_2O$ requires C, 37·7; H, 3·7; N, 29·3%). The *purine*, of unchanged m. p., was obtained from this by drying at 100° over phosphoric oxide *in vacuo* for 1 hour (Found: N, 30·7. $C_6H_6ON_4S$ requires N, 30·8%).

6-Hydroxy-8-methylthio-9-methylpurine (XIII; R = SMe).—5-Amino-2-methylthio-1-methylglyoxaline-4-carboxyamide (0·2 g.) was heated under reflux with formic acid (10 c.c.) and acetic anhydride (10 c.c.) for 2 hours, and the solution evaporated to dryness *in vacuo*. The residue (0·2 g.) was dissolved in boiling methanol (40 c.c.) and evaporation of this to small bulk (20 c.c.), followed by cooling, yielded the *purine* in clusters of colourless rods, m. p. 280—282°, which were recrystallised from methanol (Found: C, 42·6; H, 4·6; N, 28·1. $C_7H_8ON_4S$ requires C, 42·9; H, 4·2; N, 28·5%).

6-Hydroxy-9-methylpurine (XIII; R = H).—5-Amino-1-methylglyoxaline-4-carboxyamide (cf. Part IX, *loc. cit.*) (0·3 g.) was heated under reflux with acetic anhydride (5 c.c.) and formic acid (5 c.c.) for 2 hours and the solution evaporated to dryness *in vacuo*. The residue was dissolved in boiling glacial acetic acid (25 c.c.); evaporation of this mixture to a smaller bulk (15 c.c.), followed by dilution with ethanol (10 c.c.), gave the purine (0·2 g.) in colourless prisms which were recrystallised from glacial acetic acid and then had m. p. 375° (Found: C, 48·1; H, 4·0; N, 37·3. Calc. for $C_6H_6ON_4$: C, 48·0; H, 4·0; N, 37·3%).

6-Keto-2'-methylthio-1 : 6-dihydrothiazolo(5' : 4'-4 : 5)pyrimidine (XIV; R = SMe, R' = H).—(a) *By cyclisation of the* N-*formyl derivative.* 5-*N*-Formamido-2-methylthiothiazole-4-carboxyamide (0·5 g.) was covered with acetic anhydride (10 c.c.), and the whole heated under reflux for 1·5 hours, the solid gradually dissolving. The solvent was removed *in vacuo*, and the residue was dissolved in boiling ethanol (50 c.c.). The solution was evaporated to *ca.* 10 c.c., from which crystals (0·4 g.) appeared on cooling. The *thiazolopyrimidine* crystallised from glacial acetic acid in rosettes of colourless needles, m. p. 254—255° (Found: N, 20·7. $C_6H_3ON_3S_2$ requires N, 21·1%).

(b) *By use of ethyl orthoformate.* 5-Amino-2-methylthiothiazole-4-carboxyamide (0·5 g.) was covered with ethyl orthoformate (8 c.c.) and acetic anhydride (12 c.c.), and the whole heated under reflux for 2 hours, whereupon the solid dissolved. The solvent was removed *in vacuo*, and the residue was dissolved in boiling ethanol (50 c.c.) and treated as above. The product (0·4 g.) had m. p. 255°, undepressed when mixed with the compound prepared by route (*a*) (Found: C, 36·6; H, 2·5; N, 21·3. $C_6H_3ON_3S_2$ requires C, 36·2; H, 2·5; N, 21·1%).

The above compound (0·2 g.) was dissolved in N-sodium hydroxide (2 c.c.) at 40°. This solution was cooled to room temperature and shaken for 15 minutes with excess of methyl sulphate (1 c.c.). The solid which separated, *6-keto-2'-methylthio-1-methyl-1 : 6-dihydrothiazolo(5' : 4'-4 : 5)pyrimidine* (XIV; R = SMe; R' = Me) was washed with water (5 c.c.) and ether (5 c.c.) and crystallised from ethanol in colourless scintillating needles, m. p. 228—229° (Found: N, 19·9. $C_7H_7ON_3S_2$ requires N, 19·7%).

6-Keto-2'-benzylthio-1 : 6-dihydrothiazolo(5' : 4'-4 : 5)pyrimidine (XIV; R = S·CH_2Ph).—5-Amino-2-benzylthiothiazole-4-carboxyamide (0·7 g.) was heated under reflux in acetic anhydride (5 c.c.) with ethyl orthoformate (5 c.c.) for 2 hours, and the solution evaporated to dryness *in vacuo*. The residue was dissolved in boiling ethanol (25 c.c.), and evaporation of this to 10 c.c., followed by cooling, yielded the *thiazolopyrimidine* in dense clusters of colourless needles (0·8 g.) which crystallised from ethanol and then had m. p. 165° (Found: C, 52·5; H, 3·7; N, 15·4. $C_{12}H_9ON_3S_2$ requires C, 52·4; H, 3·3; N, 15·3%).

6-Keto-2'-benzyl-1 : 6-dihydrothiazolo(5' : 4'-4 : 5)pyrimidine (XIV; R = CH_2Ph).—5-Amino-2-benzylthiazole-4-carboxyamide (0·4 g.) was heated under reflux with ethyl orthoformate (4 c.c.) and acetic anhydride (4 c.c.) for 2 hours, and the excess of reactants removed *in vacuo*. The residue crystallised from methanol (*ca.* 10 c.c.), to give the *thiazolopyrimidine* (0·3 g.). This crystallised from ethanol in colourless needles, m. p. 234° (Found: C, 59·5; H, 3·9. $C_{12}H_9ON_3S$ requires C, 59·3; H, 3·7%).

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494. *The Preparation of α-N-Alkylamino-nitriles, -amides, and -acids.*

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Various α-*N*-alkylamino-nitriles have been prepared from appropriate aldehydes and amines; they are conveniently hydrolysed to the corresponding α-*N*-alkylamino-amides and -acids by concentrated sulphuric acid. In this way, the amino-acids have been obtained in overall yields of 75—80%.

α-*N*-Alkylamino-acids were required in synthetical studies related to a series of antibiotics (Cook, Cox, and Farmer, this vol., p. 1022; see also Plattner and Nager, *Helv. Chim. Acta*, 1948, **31**, 2192, 2203). Several α-*N*-alkylamino-amides and -nitriles were also required in a similar connection (Azole Series, Part XXI, succeeding paper) and it was convenient to use the same starting materials in all three cases.

N-Alkylamino-nitriles have been prepared from aldehydes and ketones by the treatment of cyanohydrins with amines (see, *inter al.*, Jacobson, *J. Amer. Chem. Soc.*, 1945, **67**, 1996) and by the reaction of Schiff's bases with hydrogen cyanide (see, *inter al.*, Trollais, *Bull. Soc. chim.*, 1947, 959) but in most cases it is convenient to avoid the isolation of the intermediate stages. One of the most satisfactory procedures is that of Knoevenagel and Mercklin (*Ber.*, 1884, **17**, 678) in which the carbonyl compound is treated with sodium hydrogen sulphite, followed by the amine and potassium cyanide. This method was used in the present work to prepare α-methylamino-*n*-valeronitrile, α-*methylamino*iso*valeronitrile*, α-iso*propylamino*-n-*valeronitrile*, and α-*iso*propyalmino*iso*valeronitrile and the first case was studied in some detail in order to ascertain the most satisfactory conditions. By use of equimolecular proportions of each reactant, the desired product was obtained in 65% yield, together with a high-boiling compound which was found to be *methyliminobis*-n-*valeronitrile*. The use of two molecular proportions of methylamine eliminated this product and gave 85% of α-methylamino-*n*-valeronitrile whilst 1·5 molecular proportions gave an 80% yield of the desired nitrile; the last proportion was used in subsequent similar preparations.

This method was not satisfactory with lower homologues of the series because the high solubility of the nitriles in water made isolation difficult. Blitz and Slotte (*J. pr. Chem.*, 1926, [ii], **113**, 252) described a preparation of methylaminoacetonitrile in which potassium cyanide was added to a mixture of formaldehyde and methylamine hydrochloride; the product, after extraction with ether, was purified by conversion into its hydrochloride. Repetition of this work, however, gave a crude oil which on distillation was found to contain a large amount of a high-boiling *compound* which appeared analytically to be derived by the elimination of water from methylaminoacetonitrile and two molecular parts of formaldehyde. On treatment with sulphuric acid in ethanol, it formed a sulphate, m. p. 160°, which proved to be the sulphate of methylaminoacetonitrile as it was also obtained from the low-boiling product, although it did not correspond with that described by Délépine (*Bull. Soc. chim.*, 1903, **29**, 1198) as "not melting below 210°." This property of aldehyde derivatives of amino-nitriles of forming salts of the parent compounds on treatment with acid is likely to be general, so that no amino-nitrile preparation in which the product is not isolated by distillation can be regarded with complete confidence.

Methylaminoacetonitrile was obtained in practically quantitative yield by the treatment of hydroxyacetonitrile with alcoholic methylamine; iso*propylaminoacetonitrile* was obtained in a similar way, and in both cases the products were isolated by fractionation of the reaction mixture. An attempt to prepare aminoacetonitrile under the same conditions gave an anomalous result. Menge (*J. Amer. Chem. Soc.*, 1934, **56**, 2197) claimed a quantitative conversion using liquid ammonia but, when the hydroxyacetonitrile was kept at 0° for 24 hours in a large excess of methanolic ammonia and the solvent removed below 50°, a yellow oil was obtained which, although it contained some aminoacetonitrile, consisted mainly of a high-boiling *compound* which polymerised when set aside for several days, even at 0°. This product was found to have the composition required of 1 mol. of amino- + 1 mol. of hydroxy-acetonitrile, and on treatment with sulphuric acid in ethanol yielded aminoacetonitrile sulphate.

This reaction appears to be peculiar to hydroxyacetonitrile since, when α-hydroxy-*n*-valeronitrile was treated with ammonia under the same conditions, α-*amino*-n-*valeronitrile* was obtained in good yield (66%) and the high-boiling by-product was the expected *iminobis*-n-*valeronitrile*. Although the amino-nitrile boiled over a narrow temperature range, it could not be obtained completely free from the imino-nitrile. This is due to the ease with which it loses ammonia, a tendency which has been noted, with similar compounds, by other workers.

The usual method for the preparation of amides of amino-acids consists in treating the corresponding esters with ammonia, but a number of by-products are formed and yields are often poor. Lipp (*Annalen*, 1880, **205**, 14) and Gulewitsch and Wasmus (*Ber.*, 1906, **39**, 1189) treated amino-nitriles with fuming hydrochloric acid and isolated the hydrochlorides of the corresponding amides from the reaction mixture, but the yields were not reported. Attempts to use this technique with methylaminoacetonitrile gave largely sarcosine and ammonium chloride, and it seemed that more closely controlled conditions were required. Tiemann and Stephan (*Ber.*, 1882, **15**, 2035) converted several arylamino-nitriles into the corresponding amides by treatment with concentrated sulphuric acid, isolating the product by pouring the reaction mixture on ice and neutralising it with ammonia; when this was done with methylaminoacetonitrile, no product could be isolated from the aqueous solution, but, if instead the sulphuric acid solution was poured into well-cooled and stirred 95% ethanol, N-*methylglycine amide hydrogen sulphate* crystallised in quantitative yield. When this salt was suspended in methanol and neutralised with sodium methoxide, removal of the sodium sulphate and evaporation gave N-*methylglycine amide* in 90% yield. Aminoacetonitrile sulphate was converted into glycine amide in the same way in 90% yield, and a similar technique was used to prepare N-iso*propylglycine amide* and N-*methylnorvaline amide*.

In view of the absence of by-products in the above reactions it seemed that this technique might usefully be employed in the hydrolysis of amino-nitriles to amino-acids. Cocker and Lapworth (*J.*, 1931, 1391) pointed out that alkaline conditions should be avoided because of the simultaneous dissociation which takes place, and recommended the use of 40% sulphuric acid. α-Methylamino-*n*-valeronitrile was hydrolysed under these conditions, and *N*-methylnorvaline was isolated in 65% yield; a non-basic oil was formed at the same time. When the nitrile was first heated with the same amount of concentrated sulphuric acid for 1 hour, the solution diluted with water to 40% sulphuric acid and boiled under reflux for 5 hours, the amino-acid was obtained in 95% yield. The hydrolysis mixture could be worked up according to the method recommended by Cocker and Lapworth (*loc. cit.*) using barium carbonate etc., but it was more convenient to add the calculated amount of sodium hydroxide and, after evaporation to dryness, to extract the amino-acid with methanol.

This hydrolysisprocedure proved to be equally satisfactory in the hydrolysis of α-*iso*propylamino-*n*-, α-methylamino*iso*-, and α-*iso*propylamino*iso*-valeronitrile. In the last two cases, the N-*methylvaline amide* and N-iso*propylvaline amide* formed during the first stage of the reaction were surprisingly resistant to hydrolysis and could be isolated on working up the product; after the mixture had been heated under reflux for 5 hours, hydrolysis was only 30% complete, and even after 16 hours 30% of the amide remained unchanged.

By the use of the methods outlined above, *N*-methylvaline, *N*-methylnorvaline, N-iso*propylvaline*, and N-iso*propylnorvaline* were obtained from the corresponding aldehydes in yields of 75—80%.

Experimental.

*Preparation of α-Methylamino-*n*-valeronitrile.*—*n*-Butyraldehyde (50 g.) was added with cooling and stirring to a solution of sodium pyrosulphite (55 g.) in water (150 c.c.). After 30 minutes, 33% aqueous methylamine (67 c.c., 1 equiv.) was run in rapidly, and after a further 30 minutes finely powdered potassium cyanide (45 g.) was added. Stirring was continued for 1 hour, whereafter the oily layer was separated and the solution extracted with ether (2 × 150 c.c.). After being dried, the solvent was removed and the product distilled *in vacuo*. The first fraction, b. p. 85°/25 mm., was α-methylamino-*n*-valeronitrile (50 g., 65%). The second fraction, b. p. 100°/10^{-3} mm., was *methyliminobis-n-valeronitrile* (13 g., 20%) (Found: C, 68·3; H, 9·7. $C_{11}H_{19}N_3$ requires C, 68·4; H, 9·8%). This experiment was repeated using 1·5 and 2 equivalents of methylamine; the yields of α-methylamino-*n*-valeronitrile were 80% and 85%, respectively, whilst the formation of the iminobisnitrile was correspondingly reduced.

*Preparation of α-Methylamino*iso-, α-iso*Propylamino*-n-, *and* α-iso*Propylamino*iso-*valeronitrile.*—The technique described above was used to prepare the three nitriles, with in each case 1·5 molecular equivalents of the necessary amine. *α-Methylamino*iso*valeronitrile*, b. p. 70°/20 mm., was obtained in 80% yield (Found: N, 25·0. $C_6H_{12}N_2$ requires N, 25·0%). α-iso*Propylamino*-n-*valeronitrile*, b. p. 86°/20 mm., was obtained in 80% yield (Found: C, 68·9; H, 11·5; N, 20·0. $C_8H_{16}N_2$ requires C, 68·6; H, 11·4; N, 20·0%). α-*iso*Propylamino*iso*valeronitrile, b. p. 86°/25 mm., was obtained in 85% yield. In each case, the product was a colourless liquid, with a pungent odour, which could be stored for several months without deterioration.

Preparation of Methylaminoacetonitrile.—Methylamine hydrochloride (100 g.) was dissolved in 40% formaldehyde solution (200 g.) and cooled to 0°; potassium cyanide (100 g.) in water (100 c.c.) was added during 3 hours with stirring. The oily layer was removed and, after being kept overnight, the solution was extracted with ether (3 × 300 c.c.). The combined product was dried and distilled, the first fraction, b. p. 65°/20 mm., being methylaminoacetonitrile (50 g., 47%). This formed a *sulphate*, m. p. 160°, which crystallised from ethanol as white needles (Found: N, 23·8.

$C_5H_8N_2,\frac{1}{2}H_2SO_4$ requires N, 23·6%). The second *fraction*, b. p. 90°/0·1 mm., amounted to 65 g. (Found: C, 53·9; H, 7·4; N, 24·9. $C_5H_8ON_2$ requires C, 53·6; H, 7·1; N, 25·0%). On treatment with ethanolic sulphuric acid, this formed the sulphate, m. p. 160°, described above.

Hydroxyacetonitrile (100 g.) was added to a solution of methylamine (80 g., 1·5 equivs.) in methanol (250 c.c.) cooled in ice. The mixture was set aside overnight and distilled. The fraction, b. p. 65—8°/20 mm., was methylaminoacetonitrile (114 g., 93%).

Preparation of iso*Propylaminoacetonitrile.*—This was obtained by treating hydroxyacetonitrile (100 g.) with *iso*propylamine (103 g., 1·5 equivs.) in methanol (250 c.c.) and setting the mixture aside for 16 hours. The *product*, b. p. 83—85°/20 mm., amounted to 155 g. (90%) (Found: C, 61·0; H, 10·3; N, 28·8. $C_5H_{10}N_2$ requires C, 61·2; H, 10·2; N, 28·6%). It was a colourless liquid with a strong basic odour.

Action of Alcoholic Ammonia on Hydroxyacetonitrile.—Hydroxyacetonitrile (30 g.) in methanol (100 c.c.) was added cautiously to liquid ammonia (100 c.c.), and the mixture was set aside for 24 hours at 0°. The excess of ammonia and methanol was then removed *in vacuo* below 50°, and the yellow oil which remained was distilled. The main *fraction*, b. p. 70—72°/1 mm., amounted to 20 g. (Found: C, 42·3; H, 6·4; N, 37·1. $C_4H_7ON_3$ requires C, 42·5; H, 6·2; N, 37·1%) whilst a thick dark residue remained in the flask. A portion of the main fraction was dissolved in ethanol and a solution of ethanolic sulphuric acid was added until the mixture was just acid to Congo-red. The white solid was purified by dissolution in the minimum amount of water, followed by addition to ethanol. It melted at 173° (decomp.) and did not depress the m. p. of an authentic specimen of aminoacetonitrile sulphate.

*Action of Alcoholic Ammonia on α-Hydroxy-*n*-valeronitrile.*—Hydroxy-*n*-valeronitrile (30 g.) in methanol (100 c.c.) was added cautiously to liquid ammonia (100 c.c.) and set aside at 0° for 24 hours. The ammonia and methanol were removed *in vacuo* below 50°, and the product distilled. The main fraction, b. p. 86°/20 mm., was *α-amino-*n*-valeronitrile* (Found: C, 62·9; H, 10·5; N, 27·3. $C_5H_{10}N_2$ requires C, 61·2; H, 10·2; N, 28·6%). It was a colourless liquid which smelled strongly of ammonia after several days at 0° and amounted to 20 g. (66%). A second fraction, b. p. 100°/10^{-5} mm., was *iminobis-*n*-valeronitrile* and weighed 7 g. (Found: C, 66·9; H, 9·7; N, 23·3. $C_{10}H_{17}N_3$ requires C, 67·0; H, 9·5; N, 23·5%).

Preparation of N*-Methylglycine Amide.*—Methylaminoacetonitrile sulphate (30 g.) was added with shaking to concentrated sulphuric acid (60 c.c.) and heated at 100° for 1 hour. It was then cooled and run into 95% ethanol (400 c.c.) with efficient stirring and cooling in ice. The *N-methylglycine amide hydrogen sulphate* which crystallised was filtered off, washed with a little ice-cold ethanol, and dried *in vacuo* (yield, 46 g., 98%). It could be recrystallised from methanol as colourless hygroscopic cubes, m. p. 102° (Found: N, 15·0. $C_5H_8ON_2,H_2SO_4$ requires N, 15·1%). The hydrogen sulphate (30 g.) was suspended in methanol (100 c.c.) and cooled in ice, and sodium methoxide in methanol was run in with stirring until the mixture was just alkaline to phenolphthalein. It was filtered to remove the sodium sulphate which was washed with more methanol, and the combined filtrates were evaporated *in vacuo*. The *N-methylglycine amide* which remained amounted to 13 g. (90%) and sublimed rapidly *in vacuo* leaving very little residue. The product was obtained as white hygroscopic prisms, m. p. 70—72° (Found: C, 40·7; H, 9·1; N, 31·6. $C_3H_6ON_2$ requires C, 40·9; H, 9·1; N, 31·8%).

Preparation of Glycine Amide, N-iso*Propylglycine Amide, and* N*-Methylnorvaline Amide.*—Glycine amide was prepared by the procedure outlined above, in 90% overall yield, from aminoacetonitrile sulphate. The product, m. p. 65—66°, did not depress the m. p. of authentic glycine amide. In the preparation of the other two amides, a clear solution was obtained on adding the sulphuric acid reaction mixture to ethanol and it was necessary to neutralise the whole of the acid. N-iso*Propylglycine amide* (91%) was obtained as white prisms, m. p. 68°, which sublimed *in vacuo* and liquefied on exposure to moist air (Found: N, 24·0. $C_5H_{12}ON_2$ requires N, 24·1%). N*-Methylnorvaline amide* (87%) also sublimed as white prisms, m. p. 102—103° (Found: C, 55·6; H, 10·9; N, 21·5. $C_6H_{14}ON_2$ requires C, 55·4; H, 10·8; N, 21·5%).

Preparation of N*-Methylnorvaline and* N-iso*Propylnorvaline.*—*α*-Methylamino-*n*-valeronitrile (50 g.) was added with cooling and stirring to concentrated sulphuric acid (90 g.), and the mixture was heated at 100° for 1 hour. Ice (70 g.) was added and the stirrer was removed after careful washing with water (50 c.c.) so that none of the acid was lost. The mixture was then heated under reflux for 5 hours, and a solution of sodium hydroxide (72·5 g., 1 equiv.) in water (150 c.c.) was added cautiously. The water was removed *in vacuo*, and the product extracted with hot methanol (4 × 300 c.c.). Evaporation of the methanol left a white solid which, after being washed with acetone (200 c.c.), was nearly pure *N*-methylnorvaline. It sublimed without melting, as white prisms (56 g., 96%). In the same way, N-iso*propylnorvaline* was obtained from *α-iso*propylamino-*n*-valeronitrile in 94% yield, as a white powder which also sublimed without melting (Found: C, 60·3; H, 10·7; N, 9·0. $C_8H_{17}O_2N$ requires C, 60·5; H, 10·7; N, 8·8%).

Preparation of N*-Methylvaline Amide and* N*-Methylvaline.*—*α*-Methylamino*iso*valeronitrile (50 g.) was hydrolysed with concentrated sulphuric acid (90 g.) according to the procedure outlined above. The extraction with methanol, however, yielded a crude product which separated into two components on being washed with acetone. The insoluble material was *N*-methylvaline (19 g., 32%) which sublimed, without melting, as white prisms. From the acetone solution, there was obtained on evaporation a thick yellow oil (37 g., 63%) which slowly crystallised and which sublimed *in vacuo* as colourless prisms, m. p. 85°. This proved to be *N-methylvaline amide* (Found: C, 55·2; H, 10·9; N, 21·2. $C_6H_{14}ON_2$ requires C, 55·4; H, 10·8; N, 21·5%). When the period of hydrolysis was extended to 18 hours, the product contained 70% of *N*-methylvaline and 25% of *N*-methylvaline amide and it was only after 40 hours that the amount of amide became unimportant.

Preparation of N-iso*Propylvaline Amide and* N-iso*Propylvaline.*—The hydrolysis of *α-iso*propylamino*iso*valeronitrile was carried out using the procedure described above. After a period of reflux of 5 hours, the products obtained were N-iso*propylvaline* (26%), which sublimed, without melting, as white prisms (Found: C, 60·7; H, 10·9; N, 8·7. $C_8H_{17}O_2N$ requires C, 60·5; H, 10·7; N, 8·8%), and N-iso*propylvaline amide* (68%), m. p. 61°, which sublimed in a high vacuum as white prisms (Found:

C, 60·9; H, 11·5; N, 17·6. $C_8H_{18}ON_2$ requires C, 60·8; H, 11·4; N, 17·7%). After a period of reflux of 16 hours, the yield of the amino-acid was 68% and that of the amide was 30%.

Grateful acknowledgement is made of the award of an Australian National University Scholarship (to S. F. C.). We also thank Sir Ian Heilbron, D.S.O., F.R.S., for his interest and encouragement.

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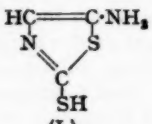
495. *Studies in the Azole Series. Part XXI. Experiments with N-Alkylamino-nitriles.*

By A. H. COOK and S. F. COX.

N-Alkylamino-nitriles react with carbon disulphide at rates depending on the substitution on the nitrogen and α-carbon atoms, the products being 5-amino-2-thio-3-alkylthiazolines. The behaviour of representative compounds towards methyl iodide, acid, and alkali is described.

IN Part III of this Series (*J.*, 1948, 201) it was shown that the reaction between aminoacetonitrile and carbon disulphide led to the formation of 5-amino-2-mercaptothiazole (I) which was converted by alkali into 2 : 4-dithiohydantoin (II; R = H) and by acid into 2-mercapto-thiazol-5-one (III). It seemed likely that certain of the properties of these and related compounds might be due to the existence of a thiol group in the 2-position and it was decided to study substances in which this structure was precluded by the presence of an alkyl group on the adjacent nitrogen atom, *e.g.*, (IV). This work also forms part of a large study of *N*-alkyl-amino-acids and their derivatives prompted by the occurrence of related compounds in certain antibiotics (Cook and Cox, this vol., p. 2347).

The initial experiments were directed towards the preparation of 5-amino-2-thio-3-methyl-thiazoline (IV; R = H) by interaction of carbon disulphide with methylaminoacetonitrile. This is stated (U.S.P. 2,143,816) to lead to the formation of 1-methyl-2 : 4-dithiohydantoin (II; R = Me), but it was considered that the conditions used in the isolation of this material (extraction with alkali) might have led to secondary changes and that the aminothiazolone might be the first product (cf. Part III, *loc. cit.*, and Carrington, *J.*, 1948, 1620). When the two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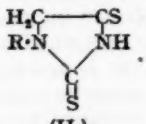
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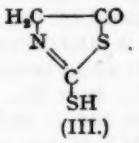
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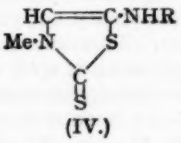
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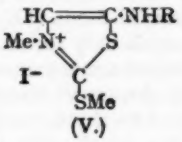
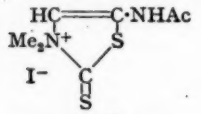

(V.)

compounds were mixed in solution, a vigorous reaction took place but the product was obtained as a gum which darkened rapidly on exposure to air or on warming it in solution. On treatment with acetic anhydride, it formed a stable crystalline derivative which yielded carbon disulphide on being heated under reflux with acid and so was formulated as *5-acetamido-2-thio-3-methyl-thiazoline* (IV; R = Ac). When the initial condensation was carried out in the presence of benzaldehyde, the Schiff's *base* of the aminothiazolone was formed. The acetyl derivative was remarkable for its ready solubility in sodium hydroxide from which it could be recovered unchanged, and an unsuccessful attempt was made to locate the active hydrogen atom by treatment with diazomethane. However, when the potassium salt was treated with methyl iodide in dry acetone, potassium iodide separated and a water-soluble product was formed. This must be considered as being a quaternary hydroxide as, on addition of hydrogen iodide, the corresponding *methiodide* was obtained; this could also be prepared directly from (IV; R = Ac) by boiling it with methyl iodide. Two structures, (V; R = Ac) and (VI), were possible for this compound, of which the first proved to be correct. Thus, on boiling it with alkali, methyl thiol was evolved, and in hot mineral acid an acid material was formed which was shown to be *N-dithiocarbomethoxy-N-methylglycine* (VII; R = Me, R′ = OH) by its synthesis from sarcosine and carbon disulphide by the method of Körner (*Ber.*, 1908, **41**, 1901). The possibility that the methyl group might have wandered under the conditions of hydrolysis was disproved by the synthesis of (V; R = Ac) by an alternative route. 5-Acetamido-2-mercaptothiazole (VIII; R = H) was treated with methyl iodide, giving the *hydriodide* of 5-acetamido-2-methyl-thiothiazole (VIII; R = Me). This dissolved in sodium hydroxide but, on addition of acetic

acid, the free *base* was liberated which reacted further with methyl iodide to give a product identical with that already obtained.

Initial attempts to prepare 2-thio-3-methylthiazolid-5-one (IX) were made by using the method which had proved most satisfactory with the unsubstituted compound. Methylaminoacetonitrile was dissolved in dry acetone, and a small amount of sodium methoxide was added, an exothermic reaction taking place with the formation of *5-imino-2 : 2 : 3-trimethyloxazolidine* (X) (cf. the behaviour of aminoacetonitrile, Part III, *loc. cit.*). However, this could not be hydrolysed easily, and under vigorous conditions the *N*-methylglycine amide formed was also decomposed, so that this approach to the amide was unsatisfactory. When *N*-methyl-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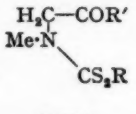
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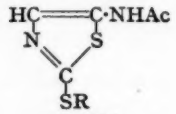
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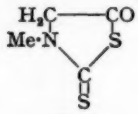
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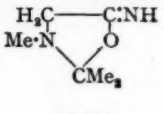
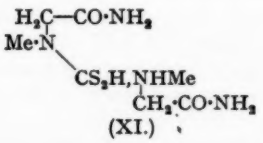

(X.)

glycine amide (prepared by another route) was treated with carbon disulphide, N-*methyl*-N-*carbamylmethylammonium* N-*methyl*-N-*carbamylmethyldithiocarbamate* (XI) was formed which on acidification was rapidly converted into *2-thio-3-methylthiazolid-5-one* (IX). A more convenient preparation consisted in treating carbon disulphide with methylaminoacetonitrile and, without isolating the aminothiazolone which was formed, pouring the mixture into acid, whereupon hydrolysis of the amino-group took place and the desired product slowly separated. On being boiled with water 2-thio-3-methylthiazolid-5-one was hydrolysed to sarcosine and carbon disulphide, and it reacted with 2 equivalents of morpholine to form the *morpholinium* salt (XII) from which it could be recovered by treatment with acid. It dissolved rapidly in sodium hydroxide solution and was recovered on acidification, behaviour which may be compared with that of (III) which cannot be recovered in this way.

An attempt was made to repeat the published preparation of 1-methyl-2 : 4-dithiohydantoin (II; R = Me) mentioned above. Under the conditions outlined in the patent, only tar was obtained but, when the aminothiazoline (IV; R = H) was prepared in methanol and two equivalents of alkali were added, removal of the solvent after 24 hours at 0° gave a water-soluble gum yielding, on acidification, a substance, m. p. 83°, which at first appeared to be the desired product. Instead of being a dithiohydantoin, however, it was identical with 2-thio-3-methylthiazolid-5-one (IX) (a possibility not precluded by the published information which included analysis only for sulphur). This behaviour is fundamentally different from that of the unsubstituted aminothiazole (I) which is split with alkali between the 1- and 2-positions, subsequent ring closure yielding the dithiohydantoin (II; R = H). It must be supposed that 5-amino-2-thio-3-methylthiazolid-5-one is split between the 1- and 5-positions with the formation of a stable alkali salt (VII; R = K, R′ = NH_2) which on acidification is converted into the thiazolidone (cf. XI). This is supported by the reaction of (VII; R = K, R′ = NH_2) with methyl iodide to give *methyl* N-*methyl*-N-*carbamylmethyldithiocarbamate* (VII; R = Me, R′ = NH_2); this was also obtained by the action of methyl iodide on (XI) and was rapidly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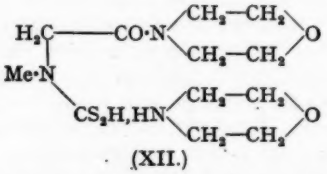
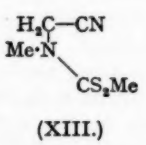

(XII.)


(XIII.)

hydrolysed on being heated with acid or alkali to give (VII; R = Me, R′ = OH). A further indication of the course of this reaction was obtained when the aminothiazoline (IV; R = H) was treated with one equivalent of alkali. Again, a water-soluble salt was obtained, but on acidification 2-thio-3-methylthiazolid-5-one was formed only slowly, and with methyl iodide a different methyl derivative was obtained. The new methyl derivative may be formulated as N-*dithiocarbomethoxy*-N-*methylaminoacetonitrile* (XIII); this was converted by hydrogen iodide into *5-amino-2-methylthio-3-methylthiazolium iodide* (V; R = H), also obtained by the action of methyl iodide on (IV; R = H).

When *iso*propylaminoacetonitrile was mixed with carbon disulphide in solution, no noticeable reaction occurred, but addition of acetic anhydride after 24 hours gave a product

which must, by analogy, be formulated as *5-acetamido-2-thio-3-isopropylthiazoline*. It was hydrolysed by acid with the liberation of carbon disulphide, and on being shaken with methyl iodide in alkaline solution afforded *5-acetamido-2-methylthio-3-isopropylthiazolium hydroxide*. This was converted into the *iodide* by treatment with hydrogen iodide, and both compounds were converted by hot acid into N-*dithiocarbomethoxy*-N-iso*propylglycine*. When *iso*propylaminoacetonitrile and carbon disulphide were mixed in the presence of benzaldehyde, the *benzylidene* derivative of the aminothiazolidine was formed. Preparation of the aminothiazolidone in solution, followed by hydrolysis with cold mineral acid, gave *2-thio-3-isopropylthiazolid-5-one*. This was hydrolysed slowly in boiling water to N-*iso*propylglycine and carbon disulphide, and, on dissolving it in sodium hydroxide and adding methyl iodide, *N*-dithiocarbomethoxy-*N-iso*propylglycine was formed. On heating a mixture of *iso*propylaminoacetonitrile and carbon disulphide in solution, a yellow *compound* slowly separated; this had a composition corresponding to $C_{10}H_{13-15}N_3S_4$ but its structure was not established. It was soluble in aqueous sodium hydroxide, from which it was recovered on acidification, and it was converted by hot acetic anhydride into the acetamidothiazolidone.

The difference in the rates of reaction of methyl- and *iso*propyl-aminoacetonitrile seemed to be sufficiently great to be worthy of further investigation and accordingly various other amino-nitriles were allowed to react with carbon disulphide. The qualitative results given below show that the groups attached to both the nitrogen atom and the α-carbon atom influence the reaction rate and that the two effects are roughly additive.

Nitrile.	Reaction rate.
Aminoacetonitrile	++++
Methylaminoacetonitrile	++++
α-Amino-*n*-valeronitrile	+++
α-Methylamino-*n*-valeronitrile	++
α-Methylamino*iso*valeronitrile	+
α-*iso*Propylaminoacetonitrile	+
α-*iso*Propylamino-*n*-valeronitrile	−
α-*iso*Propylamino*iso*valeronitrile	−

The products of these reactions were isolated as their acetyl derivatives, and their constitution as aminothiazoles was established by the formation of carbon disulphide on acid hydrolysis. From α-amino- and α-methylamino-*n*-valeronitrile, compounds formulated as *5-acetamido-2-mercapto-4-n-propylthiazole* and *5-acetamido-2-thio-3-methyl-4-n-propylthiazoline*, respectively, were obtained. In the case of α-methylamino*iso*valeronitrile, acetylation after 5 hours at 20° yielded *5-acetamido-2-thio-3-methyl-4-isopropylthiazoline*, but after 16 hours an isomeride was obtained which was considered to be *3-acetyl-1-methyl-5-isopropyl-2 : 4-dithiohydantoin*. Only starting materials could be isolated from the reactions involving the α-*iso*propylaminovaleronitriles.

Experimental.

Reactions with Methylaminoacetonitrile.—Methylaminoacetonitrile (10 g.) in ether (30 c.c.) was added under nitrogen with cooling and stirring to carbon disulphide (10·5 g., 1 equiv.) in ether (20 c.c.). A yellow gum separated which did not crystallise on prolonged scratching. On attempted crystallisation from a variety of solvents, it rapidly darkened. The reaction was repeated in the same volume of ethyl acetate; the product remained in solution and on addition of acetic anhydride (12 g.) *5-acetamido-2-thio-3-methylthiazoline* rapidly separated (20 g., 74%). This was recrystallised from ethanol as pale yellow cubes, m. p. 221° (Found: C, 38·6; H, 4·5; N, 14·8. $C_6H_8ON_2S_2$ requires C, 38·3; H, 4·3; N, 14·9%). It dissolved readily in 2N-sodium hydroxide from which it was recovered unchanged after being heated under reflux for 1 hour. When heated with 2N-hydrochloric acid, it slowly passed into solution with the formation of carbon disulphide.

Methylaminoacetonitrile (5 g.) in ethyl acetate (5 c.c.) was added with cooling to a mixture of carbon disulphide (6 g.) and benzaldehyde (8 g.) in ethyl acetate (20 c.c.). On scratching it the *benzylidene* derivative of the aminothiothiazoline separated (12 g., 70%). It crystallised from ethanol as yellow needles, m. p. 187° (Found: C, 56·7; H, 4·7; N, 12·3. $C_{11}H_{10}N_2S_2$ requires C, 56·4; H, 4·3; N, 12·0%).

5-Acetamido-2-thio-3-methylthiazoline (10 g.) was suspended in methanol (30 c.c.) and heated under reflux with methyl iodide (15 g.) for 1 hour, slowly passing into solution and being replaced by *5-acetamido-2-methylthio-3-methylthiazolium iodide* (14 g., 80%). This recrystallised from methanol as yellowish-brown cubes, m. p. 212° (Found: C, 25·7; H, 3·4; N, 8·2. $C_7H_{11}ON_2S_2I$ requires C, 25·4; H, 3·4; N, 8·5%). When the iodide (10 g.) was heated under reflux with 2N-hydrochloric acid (50 c.c.) for 1 hour, a clear solution was obtained from which *N-dithiocarbomethoxy-N-methylglycine* (4·7 g., 86%) crystallised on cooling. After recrystallisation from water as pale yellow plates, it had m. p. 148° (Found: C, 33·9; H, 5·0; N, 7·8. $C_5H_9O_2NS_2$ requires C, 33·6; H, 5·0; N, 7·8%). This product was also obtained by shaking a solution of sarcosine (1 g.) in 2N-sodium hydroxide (12 c.c.) with carbon disulphide (3 c.c.) for 8 hours; methyl iodide (2 c.c.) was then added and after being shaken for a further hour the aqueous

layer was separated and acidified. The product (1·5 g.) had m. p. 144°, undepressed on admixture with the ester above.

5-Acetamido-2-mercaptothiazole (this Series, Part III, *loc. cit.*) (5 g.) was suspended in methanol (20 c.c.) and heated under reflux with methyl iodide (8 g.) for 1 hour. The *hydriodide* of 5-acetamido-2-methylthiothiazole (7 g., 78%) crystallised as fawn-coloured needles, m. p. 207—209° (decomp.) (Found: N, 8·6. $C_6H_9ON_2S_2I$ requires N, 8·9%). It dissolved readily in 2N-sodium hydroxide and, on acidification with acetic acid, *5-acetamido-2-methylthiothiazole* was formed, which crystallised from ethanol–water as pale brown needles, m. p. 145° (Found: C, 38·3; H, 4·4; N, 15·1. $C_6H_8ON_2S_2$ requires C, 38·3; H, 4·3; N, 14·9%). When heated under reflux with methyl iodide in methanol, this was converted into the methiodide of 5-acetamido-2-methylthiothiazole, identical with that described above.

Methylaminoacetonitrile (20 g.) was mixed with dry acetone (30 c.c.), and a small amount of sodium methoxide added. An exothermic reaction commenced after which the solution was heated under reflux for 30 minutes. Evaporation *in vacuo* gave a yellow oil which slowly crystallised. This was *5-imino-2 : 2 : 3-trimethyloxazolidine* and crystallised from *iso*propyl ether as pale yellow cubes, m. p. 73° (Found: C, 55·9; H, 9·2; N, 22·2. $C_6H_{10}ON_2$ requires C, 56·2; H, 9·4; N, 21·9%). When this product (10 g.) was dissolved in water (20 c.c.) and heated on a steam-bath, acetone was slowly formed and later ammonia was evolved. Evaporation after 2 hours gave an oil (8 g.) which solidified after distillation at 100°/10^{-5} mm. and was a mixture of *N*-methylglycine amide and unchanged oxazolidine. Pure *N*-methylglycine amide (5 g.) was treated with carbon disulphide (2·5 g.) in methanol (15 c.c.); on cooling and scratching, *N-methyl-N-carbamylmethylammonium N-methyl-N-carbamylmethyldithiocarbamate* separated as pale yellow prisms, m. p. 134° (6·5 g., 90%) (Found: C, 33·7; H, 6·3; N, 21·9. $C_7H_{16}O_2N_4S_2$ requires C, 33·3; H, 6·3; N, 22·2%). When the dithiocarbamate (5 g.) was dissolved in water (25 c.c.) at 0° and acidified with concentrated hydrochloric acid (10 c.c.), *2-thio-3-methylthiazolid-5-one* (2·1 g., 72%) rapidly separated as pale yellow plates. The product had m. p. 78° which was not elevated by recrystallisation from several solvents but a portion sublimed in a high vacuum had m. p. 84° (Found: N, 9·6. $C_4H_5ONS_2$ requires N, 9·5%).

Methylaminoacetonitrile (10 g.) in methanol (10 c.c.) was added, with cooling and stirring under nitrogen, to carbon disulphide (10·5 g.) in methanol (10 c.c.). After 30 minutes, the mixture was poured into ice-cold 4N-hydrochloric acid (150 c.c.) and shaken vigorously for 5 minutes. It was then filtered and after 3 hours at 0° the product was collected, washed with water, and dried *in vacuo* (yield, 13 g., 63%). The product (10 g.) was heated under reflux with water (50 c.c.) for 1 hour, slowly dissolving with the formation of carbon disulphide. Evaporation *in vacuo* gave a gum which crystallised from ethanol as colourless prisms, m. p. 209—211° (3·5 g., 60%). The product did not depress the m. p. of an authentic specimen of sarcosine on admixture.

2-Thio-3-methylthiazolid-5-one (2 g.) in acetone (10 c.c.) was treated with morpholine (2·4 g., 2 equivs.). The mixture became warm and the *morpholinium* salt (XII) of *N*-dithiocarboxy-*N*-methylaminoacetomorpholide (4 g., 90%) separated as pale yellow prisms, m. p. 175—180° (decomp.) (Found: N, 12·9. $C_{12}H_{23}O_3N_3S_4$ requires N, 13·1%). This was readily soluble in water and on acidification the thiazolidone was reformed. 2-Thio-3-methylthiazolid-5-one (1 g.) was shaken with N-sodium hydroxide (14 c.c., 2 equivs.) in which it rapidly dissolved. After 15 minutes, the solution was acidified and the thiazolidone (0·8 g.) recovered.

Methylaminoacetonitrile (10 g.) in methanol (10 c.c.) was added under nitrogen with cooling and stirring to carbon disulphide (10·5 g.) in methanol (20 c.c.). After 30 minutes, potassium hydroxide (16 g.) in methanol (50 c.c.) was added. The solution, which became dark brown, was set aside at 0° for 24 hours and evaporated *in vacuo*. The gum which remained was dissolved in water (200 c.c.) and divided into two equal portions. To the first was added concentrated hydrochloric acid (20 c.c.), a pale brown solid rapidly separating. This was filtered off and washed with water; it proved to be 2-thio-3-methylthiazolid-5-one (8 g., 78%) and did not depress the m. p. of an authentic specimen. The other portion of aqueous solution was shaken with methyl iodide (20 g.), a brown solid being formed. It crystallised from methanol as colourless needles, m. p. 152°, and proved to be *methyl* N-*methyl*-N-*carbamylmethyldithiocarbamate* (10 g., 78%) (Found: C, 33·6; H, 5·4; N, 15·4. $C_5H_{10}ON_2S_2$ requires C, 33·6; H, 5·6; N, 15·7%). The same product was formed when *N*-methyl-*N*-carbamylmethylammonium *N*-methyl-*N*-carbamylmethyldithiocarbamate (1 g.) was dissolved in water (5 c.c.) and shaken with methyl iodide (1 g.) (yield, 0·6 g.).

Methylaminoacetonitrile (10 g.) in methanol (10 c.c.) was added in portions to carbon disulphide (10·5 g.) in methanol (20 c.c.) cooled in ice and in an atmosphere of nitrogen. After 30 minutes, potassium hydroxide (8 g.) was added and, after a further hour the solution was evaporated *in vacuo*. The gum was dissolved in water (200 c.c.) and divided into two equal portions. The first was shaken with 4N-hydrochloric acid (60 c.c.) cooled in ice; the solid which first separated dissolved to be replaced by 2-thio-3-methylthiazolid-5-one (7 g., 67%). The second portion was shaken with methyl iodide (20 g.); a brown oil separated which slowly solidified. It crystallised from methanol as pale brown plates, m. p. 74°, and was N-*dithiocarbomethoxy*-N-*methylaminoacetonitrile* (yield, 8·5 g., 73%) (Found: C, 37·8; H, 5·3; N, 17·7. $C_5H_8N_2S_2$ requires C, 37·5; H, 5·0; N, 17·5%). This product (1 g.) was shaken with 2N-hydriodic acid (10 c.c.) for 1 hour; it slowly dissolved to be replaced by *5-amino-2-methylthio-3-methylthiazolium iodide* (1·5 g.) which crystallised from ethanol as pale yellow needles, m. p. 150° (Found: C, 21·2; H, 3·3; N, 9·6. $C_5H_9N_2S_2I$ requires C, 20·9; H, 3·1; N, 9·7%). Methylaminoacetonitrile (5 g.) in ethyl acetate (5 c.c.) was added with shaking and cooling to carbon disulphide (5·3 g.) in ethyl acetate (10 c.c.). After 30 minutes, methyl iodide (12 g.) was added and the mixture shaken vigorously as an oil separated. The oil rapidly solidified and the product (10 g., 70%) was identical with that last described.

Reactions with iso*Propylaminoacetonitrile.*—Carbon disulphide (8 g.) and *iso*propylaminoacetonitrile (10 g.) were mixed in ethyl acetate (30 c.c.) and set aside at 20° for 16 hours; acetic anhydride (10 g.) was added; *5-acetamido-2-thio-3-isopropylthiazoline* (11 g., 50%) slowly crystallised. It recrystallised from ethyl acetate as yellowish-brown needles, m. p. 163° (Found: C, 44·7; H, 5·5; N, 12·9. $C_8H_{12}ON_2S_2$ requires C, 44·4; H, 5·6; N, 13·0%). The yield was improved to 68% if the initial reaction

mixture contained acetone (10 g.); it is likely that the aminothiazolone was stabilised as its acetone Schiff's base which was later decomposed by the acetic anhydride. The acetamidothiazoline was soluble in sodium hydroxide from which it was recovered on acidification, and with boiling hydrochloric acid evolved carbon disulphide.

*iso*Propylaminoacetonitrile (5 g.) in ethyl acetate (25 c.c.) was mixed with carbon disulphide (4 g.) and benzaldehyde (7 g.). After 20 hours, the *benzylidene* derivative of the aminothiothiazoline was collected (9 g., 68%) and recrystallised from ethanol as yellow plates, m. p. 116° (Found: C, 59·6; H, 5·5; N, 10·7. $C_{13}H_{14}N_2S_2$ requires C, 59·5; H, 5·3; N, 10·7%).

5-Acetamido-2-thio-3-*iso*propylthiazoline (10 g.) was dissolved in 2N-sodium hydroxide (23 c.c.) and shaken with methyl iodide (7 g.). After 1 hour, 5-*acetamido*-2-*methylthio*-3-iso*propylthiazolium hydroxide* (10 g., 86%) was collected and recrystallised from ethyl acetate as pale yellow needles, m. p. 83° (Found: C, 43·3; H, 6·3; N, 10·9. $C_9H_{16}O_2N_2S_2$ requires C, 43·5; H, 6·5; N, 11·3%). When shaken with 2N-hydriodic acid, this was converted into the corresponding *iodide* which crystallised from ethanol–ethyl acetate as yellow prisms, m. p. 182—183° (Found: C, 30·1; H, 4·2; N, 7·5. $C_9H_{15}ON_2S_2I$ requires C, 30·2; H, 4·2; N, 7·8%). When the hydroxide (10 g.) was heated under reflux with 2N-hydrochloric acid (50 c.c.) for 1 hour, an oil formed which solidified on cooling (7 g., 81%). It crystallised from water as colourless plates, m. p. 161°, and was N-*dithiocarbomethoxy*-N-iso*propylglycine* (Found: C, 40·9; H, 6·3; N, 6·8. $C_7H_{13}O_2NS_2$ requires C, 40·6; H, 6·3; N, 6·8%).

A mixture of *iso*propylaminoacetonitrile (10 g.) and carbon disulphide (7·5 g.) in acetone (20 c.c.) was set aside at 20° for 16 hours and then shaken with ice-cold 4N-hydrochloric acid (120 c.c.). The product was filtered after 10 minutes and set aside at 0°; 2-*thio*-3-iso*propylthiazolid*-5-*one* slowly crystallised out. This was collected, washed with water, and dried *in vacuo* (yield, 12 g., 67%). A portion after sublimation in a high vacuum had m. p. 104° (Found: C, 41·2; H, 5·3; N, 7·7. $C_6H_9ONS_2$ requires C, 41·1; H, 5·1; N, 8·0%). The thiazolone (2 g.) dissolved when shaken with N-sodium hydroxide (25 c.c.); methyl iodide (2 g.) was added and, on further shaking, *N*-dithiocarbomethoxy-*N*-*iso*propylglycine (2 g.) was formed; this did not depress the m. p. of the product obtained above.

*iso*Propylaminoacetonitrile (10 g.) and carbon disulphide (15 g.) in ethyl acetate (30 c.c.) were heated under reflux for 3 hours in an atmosphere of nitrogen. The pale yellow *compound* which separated was filtered (yield, 4 g.) and recrystallised unchanged by dissolution in concentrated aqueous ammonia, followed by partial evaporation, as pale yellow prisms, m. p. 223° (Found: C, 39·6; H, 4·6; N, 13·7. $C_{10}H_{13}N_3S_4$ requires C, 39·6; H, 4·3; N, 13·9. $C_{10}H_{15}N_3S_4$ requires C, 39·4; H, 4·9; 13·8%). After this product (2 g.) had been heated with acetic anhydride (10 c.c.) at 100° for 30 minutes, cooling and scratching it yielded 5-acetamido-2-thio-3-*iso*propylthiazolid-5-one (0·8 g.).

Observations on Relative Reactivity of Several Amino-nitriles. The procedure used in each case was to add carbon disulphide (2 g.) in ethyl acetate (2 c.c.) to the amino-nitrile (1 equiv.) in ethyl acetate (2 c.c.) at 20°. The results were as follows:

Aminoacetonitrile: vigorous ebullition.

Methylaminoacetonitrile: vigorous ebullition.

α-Amino-*n*-valeronitrile: mild ebullition. Addition of acetic anhydride (2 g.) after 30 minutes caused the formation of 5-*acetamido*-2-*mercapto*-4-n-*propylthiazole* (2·2 g.) which crystallised from ethanol–ethyl acetate as pale yellow prisms, m. p. 208° (Found: C, 44·5; H, 5·6; N, 12·8. $C_8H_{12}ON_2S_2$ requires C, 44·4; H, 5·6; N, 13·0%).

α-Methylamino-*n*-valeronitrile: solution became warm. Addition of acetic anhydride (2 g.) after 30 minutes gave 5-*acetamido*-2-*thio*-3-*methyl*-4-n-*propylthiazoline* (3 g.). This was recrystallised from ethanol as yellow leaflets, m. p. 211° (Found: C, 47·2; H, 6·3; N, 12·2. $C_9H_{14}ON_2S_2$ requires C, 47·0; H, 6·1; N, 12·2%).

α-Methylamino*iso*valeronitrile: no heat of reaction detected. Addition of acetic anhydride (2 g.) after 5 hours caused the slow crystallisation of 5-*acetamido*-2-*thio*-3-*methyl*-4-iso*propylthiazoline* (2 g.). This was recrystallised from ethanol as pale yellow cubes, m. p. 168° (Found: C, 47·3; H, 6·1; N, 12·0). When addition of the acetic anhydride was delayed for 16 hours, the product was 3-*acetyl*-1-*methyl*-5-iso*propyl*-2:4-*dithiohydantoin* (1·8 g.) which recrystallised from glacial acetic acid as colourless cubes, m. p. 213° (Found: C, 47·3; H, 6·3; N, 11·9. $C_9H_{14}ON_2S_2$ requires C, 47·0; H, 6·1; N, 12·2%).

*iso*Propylaminoacetonitrile: no heat of reaction detected.

α-*iso*Propylamino-*n*-valeronitrile: unchanged starting materials recovered after 2 weeks.

α-*iso*Propylamino*iso*valeronitrile: no change after 2 weeks.

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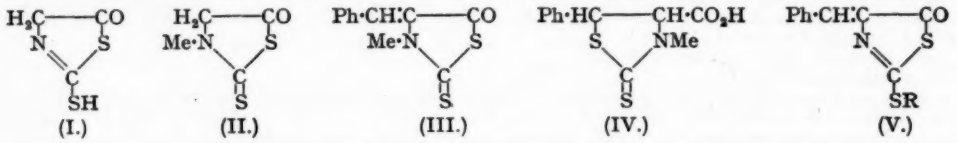
496. *Studies in the Azole Series. Part XXII. The Synthesis of N-Alkylamino-acids.*

By A. H. Cook and S. F. Cox.

The condensation of aldehydes and ketones with 2-thio-3-methylthiazolid-5-one (II), 5-acetamido-2-thio-3-methylthiazoline (VI), and several 3-substituted 2-thio-1-alkylhydantoins (XIV), and the conversion of the products into *N*-alkylamino-acids have been studied. It is concluded that, for steric and other reasons, no single azole satisfies completely the requirements of a general synthesis of *N*-alkylamino-acids although individual acids are obtainable by selecting the appropriate heterocyclic intermediates.

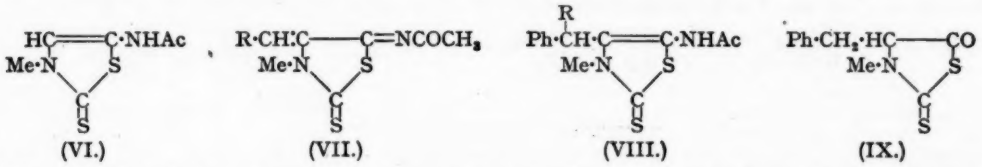
Many of the methods used for the formation of amino-acids involve an intermediate containing potential amino- and carboxy-groups to which a substituent corresponding to the side chain of the amino-acid is attached. For such a synthesis to be of preparative value, the intermediate should be stable, easily prepared, and readily convertible into the substituted product which must be easily separable from any uncondensed material; further, the condensation product should be convertible without difficulty into the corresponding amino-acid. No such general method for the synthesis of *N*-alkylamino-acids has been described in the literature. Various azoles which are potentially useful as intermediates in this connection are considered below.

2-Mercaptothiazol-5-one (I) has been shown (Part XIX, this vol., p. 2323) to be the basis of a convenient synthesis of amino-acids, and the first compound to be investigated in the present work was the related 2-thio-3-methylthiazolid-5-one (II). This condensed with benzaldehyde when heated in acetic acid containing morpholine, with the formation of *2-thio-4-benzylidene-3-methylthiazolid-5-one* (III) which was converted into β-phenyl-*N*-methyl-α-alanine by boiling hydriodic acid and red phosphorus; treatment with alkali rearranged the compound (III) to *2-thio-5-phenyl-3-methylthiazolidine-4-carboxylic acid* (IV). Unlike the unmethylated



compound, however, 2-thio-3-methyl-4-benzylidenethiazolid-5-one did not crystallise from the reaction mixture on cooling, so that its isolation in a pure state was rather tedious, and it was relatively low melting. *n*-Butyraldehyde appeared to undergo condensation with 2-thio-3-methylthiazolid-5-one in acetic acid solution but the product was a dark oil which could not be induced to crystallise, and acetone, under a variety of conditions, yielded only unchanged starting materials. These difficulties made it clear that 2-thio-3-methylthiazolid-5-one did not form the basis of a useful general method for the synthesis of *N*-alkylamino-acids, whilst an attempt to avoid its use as in the methylation of 2-mercapto-4-benzylidenethiazol-5-one (V; R = H) led only to the S-methyl *derivative* (V; R = Me).

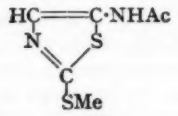
5-Amino-2-thio-3-methylthiazoline condenses with aldehydes to form the corresponding Schiff's bases, but it was thought that by using instead its acetyl derivative (VI) a product of type (VII) might be obtained. 5-Acetamido-2-thio-3-methylthiazoline (VI) did not react



with benzaldehyde in hot acetic acid containing sodium acetate, but, when the two compounds were heated under reflux in pyridine containing one equivalent of piperidine, a product crystallised from the reaction mixture which from its analysis must be *5-acetamido-2-thio-4-α-piperidinobenzyl-3-methylthiazoline* (VIII; R = N<[CH$_2$]$_5$). This compound was stable in alkaline solution but was hydrolysed when warmed with dilute acid; on treatment with alcoholic hydrogen chloride, it formed a hydrochloride from which the parent compound was recovered by ammonia. When heated under reflux with hydriodic acid and red phos-

phorus for 16 hours, (VIII; R = N<[CH$_2$]$_5$) was converted into β-phenyl-*N*-methylalanine, interruption of the reaction after 5 hours affording the intermediate 2-*thio*-4-*benzyl*-3-*methylthiazolid*-5-*one* (IX). On repetition of the condensation with morpholine instead of piperidine, 5-*acetamido*-2-*thio*-4-α-*morpholinobenzyl*-3-*methylthiazoline* (VIII; R = N<[CH$_2$·CH$_2$]$_2$>O) was formed, but with diethylamine only unchanged starting material was recovered. A mixture of benzaldehyde and piperidine in pyridine condensed similarly with 5-acetamido-2-methylthiothiazole (X) to form 5-*acetamido*-2-*methylthio*-4-α-*piperidinobenzylthiazole*. The compound (VI) appeared to condense with *n*-butyraldehyde in presence of piperidine and pyridine, but the product was a dark gum, and likewise no satisfactory condensation could be affected between acetone and (VI) under these conditions, so that the usefulness of this method also was limited.

During one of the condensations of benzaldehyde with (VI) in the presence of piperidine, the reaction mixture was distilled in steam, and a white crystalline material was observed in the distillate. Examination of this compound showed it to be benzylidenebis-1-piperidine (XI; R = N<[CH$_2$]$_5$), a product obtained by Laun (*Ber.*, 1884, **17**, 678) by heating benzaldehyde with piperidine in a sealed tube, which he described as unstable and rapidly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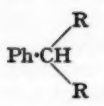
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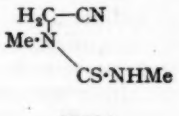
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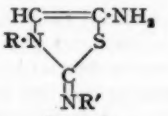
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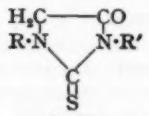
(XIV.)

hydrolysed by water. It was more conveniently obtained by boiling the two components for a few minutes in pyridine and crystallised from the mixture on cooling it in ice. It reacted with (VI) in hot pyridine and may be presumed to be the intermediate in the reactions described above. No product separated on heating a mixture of morpholine and benzaldehyde in pyridine, but fractional distillation gave *benzylidenebis*-4-*morpholine* (XI; R = morpholino). It is significant that diethylamine, which did not induce a reaction between benzaldehyde and (VI), appeared not to react with benzaldehyde in pyridine, fractionation of the reaction mixture yielding only unchanged materials.

Boyd and Robson (*Biochem. J.*, 1935, **29**, 546) obtained condensation products from aromatic aldehydes and acetyl-2-thiohydantoin under basic conditions in excellent yields, and converted the products into amino-acids. The use of the corresponding 2-thio-1-alkylhydantoins was not attempted in this work as these can not be conveniently obtained from *N*-alkylamino-nitriles, but Delépine (*Bull. Soc. chim.*, 1903, **29**, 1198) described a synthesis of 2-thio-1 : 3-dimethylhydantoin (XIV; R = R′ = Me) starting with methylaminoacetonitrile and methyl *iso*thiocyanate although he did not identify the intermediate material. When the two components were mixed in ether, a *product* was obtained which might be formulated as (XII) or (XIII; R = R′ = Me) (cf. Part IX, *J.*, 1948, 2028); the former was considered to be correct as the substance failed to give an acetyl or benzylidene derivative under appropriate conditions. On being heated with aqueous acid, it was converted into 2-thio-1 : 3-dimethylhydantoin, the overall yield being 85%. The thiohydantoin condensed smoothly with benzaldehyde in hot pyridine containing morpholine, to form 2-*thio*-5-*benzylidene*-1 : 3-*dimethylhydantoin*, and with acetone similarly to give 2-*thio*-1 : 3-*dimethyl*-5-iso*propylidene*-*hydantoin*. The use of other carbonyl compounds, however, afforded only gummy products and accordingly it was decided to investigate the use of intermediates derived from phenyl *iso*thiocyanate as these were expected to have higher m. p., and to be less soluble in organic solvents, than those obtained from methyl *iso*thiocyanate.

Phenyl *iso*thiocyanate reacted readily with methylaminoacetonitrile, and the fact that the product had cyclised was established by the ease with which it formed an *acetyl* derivative. 5-*Amino*-2-*anilo*-3-*methylthiazoline* (XIII; R = Me, R′ = Ph), obtained in this way, was converted into 2-*thio*-3-*phenyl*-1-*methylhydantoin* (XIV; R = Me, R′ = Ph) on being heated with hydrochloric acid, and the thiohydantoin condensed with benzaldehyde, *n*-butyraldehyde, or acetone to give 2-*thio*-3-*phenyl*-5-*benzylidene*-1-*methylhydantoin*, 2-*thio*-3-*phenyl*-1-*methyl*-5-*n*-*butylidenehydantoin*, and 2-*thio*-3-*phenyl*-1-*methyl*-5-iso*propylidenehydantoin*, respectively, in excellent yields. It was hoped to convert these products directly into the corresponding amino-acids by reductive hydrolysis, using hydriodic acid and red phosphorus, but, when the benzylidenehydantoin was heated under reflux with 25% hydriodic acid in acetic acid for 24 hours, 2-*thio*-3-*phenyl*-5-*benzyl*-1-*methylhydantoin* was obtained in good yield. This was

hydrolysed to β-phenyl-*N*-methylalanine under alkaline conditions, and the overall yield in the degradation was 74%. In the same way, 2-thio-3-phenyl-1-methyl-5-*iso*propylidenehydantoin was reduced to 2-*thio*-3-*phenyl*-1-*methyl*-5-iso*propylhydantoin* and hydrolysed with alkali to *N*-methylvaline.

In order to examine possible further application of this method, *iso*propylaminoacetonitrile was treated with phenyl *iso*thiocyanate in ether, the 5-*amino*-2-*anilo*-3-iso*propylthiazoline* (XIII; R = Pr^i, R′ = Ph) which was formed being hydrolysed with acid to 2-*thio*-3-*phenyl*-1-iso*propylhydantoin* (XIV; R = Pr^i, R′ = Ph). This hydantoin was condensed with benzaldehyde in a mixture of pyridine and morpholine to form 2-*thio*-3-*phenyl*-5-*benzylidene*-1-iso*propylhydantoin*, which was reduced to 2-*thio*-3-*phenyl*-5-*benzyl*-1-iso*propylhydantoin* and hydrolysed with alkali to 2-*phenyl*-N-iso*propylalanine*. In the same way, *n*-butyraldehyde yielded 2-*thio*-3-*phenyl*-1-iso*propyl*-5-n-*butylidenehydantoin*, 2-*thio*-3-*phenyl*-1-iso*propyl*-5-n-*butylhydantoin*, and N-iso*propylnorleucine*. Acetone, however, could not be condensed with the parent thiohydantoin even when the reaction period was extended from 1 to 24 hours. Similar differences in the ease of condensation of hydantoins and thiohydantoins with aldehydes and ketones have been recorded by a number of workers, but the conditions used have varied to such an extent that it is difficult to judge the exact effect of the factors involved. In the present work, it was found that the use of sodium acetate in acetic acid instead of a medium consisting of morpholine and pyridine did not affect the condensation of 2-thio-3-phenyl-1-methylhydantoin with benzaldehyde but prevented the reaction with acetone. The corresponding hydantoin did not react with either benzaldehyde or acetone in the presence of morpholine in pyridine as the condensing agent. It seems from these results that four factors can be distinguished in this type of condensation: (1) the reactivity of the carbonyl compound; (2) the reactivity of the methylene group which is adversely affected by the replacement of sulphur by oxygen; (3) a steric effect involving the group attached to the nitrogen atom adjacent to the methylene group; and (4) the efficiency of the condensing agent, morpholine in pyridine being more effective than sodium acetate in acetic acid. It must be concluded that this third method for the synthesis of *N*-alkylamino-acids does not have the desired general applicability and suffers from the necessity of converting the condensation product into the amino-acid in two steps; it is useful, however, for preparing a wide range of these amino-acids and good yields are obtained at each stage.

Experimental.

Reactions with 2-*Thio*-3-*methylthiazolid*-5-*one*.—The thiazolidone (5 g.) was heated under reflux for 2 hours with benzaldehyde (4 g.) in acetic acid (25 c.c.) containing several drops of morpholine. The solvent was removed *in vacuo* leaving a thick dark residue; after several crystallisations from aqueous ethanol, 2-*thio*-4-*benzylidene*-3-*methylthiazolid*-5-*one* was obtained as orange prisms, m. p. 117° (5·5 g., 68%) (Found: C, 56·6; H, 4·0; N, 6·2. $C_{11}H_9ONS_2$ requires C, 56·2; H, 3·8; N, 6·0%). The benzylidene compound (10 g.) was dissolved in acetic acid (30 c.c.) containing 57% hydriodic acid (12 c.c.) and red phosphorus (2 g.) and refluxed for 8 hours. The mixture was cooled, filtered, and evaporated to dryness *in vacuo*. Water (100 c.c.) was added and, after being heated (charcoal) for several minutes on a steam-bath, the mixture was filtered, made alkaline with ammonia, and evaporated to 100 c.c. On cooling, β-phenyl-*N*-methylalanine separated as white plates which were collected and washed with water. The product sublimed without melting (yield, 5·5 g., 72%). A mixture of 2-thio-4-benzylidene-3-methylthiazolid-5-one (2 g.) and potassium hydroxide (0·6 g.) in methanol (10 c.c.) was kept at 20° for 18 hours. It was evaporated *in vacuo*, dissolved in water (10 c.c.), extracted with ethyl acetate (10 c.c.), acidified, and re-extracted with ethyl acetate (10 c.c.). Evaporation gave a gum which crystallised from aqueous ethanol as pale brown prisms of 2-*thio*-5-*phenyl*-3-*methylthiazolidine*-4-*carboxylic acid*, m. p. 177° (1·6 g., 75%) (Found: C, 52·2; H, 4·6; N, 5·5. $C_{11}H_{11}O_2NS_2$ requires C, 52·2; H, 4·3; N, 5·5%).

2-Thio-3-methylthiazolid-5-one (5 g.) and *n*-butyraldehyde (5 c.c.) in acetic acid (25 c.c.) containing two drops of morpholine, were heated on the steam-bath for 2 hours. Evaporation *in vacuo* gave a dark oil which did not crystallise if seeded by the starting material or otherwise treated. 3-Methylthiazolone (5 g.) in acetic acid (20 c.c.) and acetone (10 c.c.) containing 2 drops of morpholine was heated under reflux for 2 hours. On being cooled and diluted with water, the starting material was recovered unchanged. No condensation was effected using sodium acetate in acetic acid or on heating the thiazolone in acetone containing fused zinc chloride.

2-Mercapto-4-benzylidenethiazol-5-one (Part III, *J.*, 1948, 201) was unaffected by prolonged heating with methyl iodide or methyl sulphate in ethanol. The benzylidenethiazolone (5 g.) was dissolved in N-sodium hydroxide (23 c.c., 1 equiv.) and shaken with methyl iodide (5 g.); the oily solid which separated was collected after 30 minutes and crystallised from ethanol. 2-*Methylthio*-4-*benzylidenethiazol*-5-*one* was obtained as golden needles, m. p. 99—100° (5 g., 94%) (Found: C, 56·2; H, 4·1; N, 5·9. $C_{11}H_9ONS_2$ requires C, 56·2; H, 3·8; N, 6·0%).

Reactions with 5-*Acetamido*-2-*thio*-3-*methylthiazoline*.—The acetamidothiazoline (10 g.) in pyridine (20 c.c.) containing benzaldehyde (8 g.) and piperidine (8 g.) was heated under reflux for 1 hour. On cooling, 5-*acetamido*-2-*thio*-4-α-*piperidinobenzyl*-3-*methylthiazoline* (15 g., 81%) crystallised from the

mixture; this was collected and washed with ethyl acetate. A sample recrystallised from pyridine as pale yellow cubes, m. p. 208° (Found: C, 59·8; H, 6·5; N, 11·4. $C_{18}H_{22}ON_2S_2$ requires C, 59·9; H, 6·4; N, 11·6%). The crude product (15 g.) was dissolved in acetic acid (60 c.c.) containing 57% hydriodic acid (20 c.c.) and red phosphorus (4 g.) and heated under reflux for 20 hours. The mixture was cooled, filtered, and evaporated to dryness *in vacuo*; water (100 c.c.) and charcoal (0·5 g.) were added and the solution was heated on the steam-bath for 5 minutes, filtered, and made alkaline with ammonia. On partial evaporation (to 100 c.c.) and cooling, β-phenyl-*N*-methylalanine crystallised as white plates (6 g., 77%); these were washed with water; they sublimed without melting. This experiment was repeated, the product being examined after 5 hours' heating. The phosphorus was removed from the hot solution, and on cooling *2-thio-4-benzyl-3-methylthiazolid-5-one* (3·5 g.) was obtained. This recrystallised from methanol as pale yellow prisms, m. p. 113° (Found: C, 55·7; H, 4·9; N, 5·8. $C_{11}H_{11}ONS_2$ requires C, 55·7; H, 4·6; N, 5·9%).

The acetamidothiazoline (10 g.) in pyridine (20 c.c.) containing benzaldehyde (8 g.) and morpholine (8 g.) was boiled under reflux for 1 hour. On cooling, *5-acetamido-2-thio-4-α-morpholinobenzyl-3-methylthiazoline* (14·5 g., 78%) was obtained; a portion was recrystallised from pyridine as pink cubes, m. p. 225° (Found: C, 56·1; H, 5·8; N, 11·6. $C_{17}H_{21}O_2N_3S_2$ requires C, 56·0; H, 5·8; N, 11·6%). 5-Acetamido-2-methylthiothiazole (5 g.) in pyridine (10 c.c.) containing benzaldehyde (4 g.) and piperidine (4 g.) was heated under reflux for 1 hour. The solution remained clear on cooling, but on evaporation *in vacuo* and crystallisation of the product from methanol *5-acetamido-2-methylthio-4-α-piperidinobenzylthiazole* was obtained as colourless cubes, m. p. 141° (6 g., 65%) (Found: C, 60·3; H, 6·4; N, 11·4. $C_{18}H_{23}ON_3S_2$ requires C, 59·9; H, 6·4; N, 11·6%).

The acetamidothiazoline (10 g.) in pyridine (20 c.c.) containing *n*-butyraldehyde (8 g.) and piperidine (8 g.) was heated under reflux for 1 hour. No product was obtained on cooling, and evaporation *in vacuo* gave a dark gum which could not be crystallised from a variety of solvents. Acetone, under the same conditions, yielded the unchanged starting material even when the period of reflux was extended to 24 hours.

A mixture of benzaldehyde (7 g.) and piperidine (10 g.) in pyridine (20 c.c.) was boiled under reflux for 15 minutes and then cooled in ice; benzylidenebis-1-piperidine (11 g., 72%) separated and recrystallised from light petroleum as colourless laths, m. p. 81° (Laun, *loc. cit.*, gives m. p. 80°) (Found: C, 79·3; H, 9·9; N, 11·1. Calc. for $C_{17}H_{26}N_2$: C, 79·1; H, 10·1; N, 10·9%). The compound had an odour of benzaldehyde but could be distilled in steam without appreciable decomposition; it was hydrolysed rapidly on warming it with dilute acid. 5-Acetamido-2-thio-3-methylthiazoline (5 g.) was heated with benzylidenebis-1-piperidine (7 g.) in pyridine (15 c.c.) for 1 hour; on cooling, 5-acetamido-2-thio-4-α-piperidinobenzyl-3-methylthiazoline (7 g.) was obtained.

Benzaldehyde (7 g.) and morpholine (10 g.) in pyridine (20 c.c.) were boiled under reflux for 15 minutes; the reaction mixture remained clear on cooling, but after distillation *in vacuo* a fraction, b. p. 100—120°/20 mm., solidified on being shaken with water. On recrystallisation from light petroleum, *benzylidenebis-4-morpholine* was obtained as colourless prisms, m. p. 105° (5 g., 33%) (Found: C, 69·0; H, 8·4; N, 11·0. $C_{15}H_{22}O_2N_2$ requires C, 68·7; H, 8·4; N, 10·7%). When the same procedure was used with benzaldehyde and diethylamine, only starting materials were recovered.

Reactions with Methyl iso*Thiocyanate.*—Methylaminoacetonitrile (5 g.) in ether (10 c.c.) was added with cooling and stirring under nitrogen to methyl *iso*thiocyanate (5 g.) in ether (10 c.c.). The white solid (9 g., 90%) which slowly separated was collected after 1 hour and washed with a little ether. A sample was recrystallised from ethanol and *NN'-dimethylthioureidoacetonitrile* was obtained as needles, m. p. 112° (Found: C, 42·3; H, 6·4; N, 29·6. $C_5H_9N_3S$ requires C, 42·0; H, 6·3; N, 29·4%). The crystallisation was accompanied by considerable coloration of the solution, and the solid material decomposed when stored at room temperature. The thiourea (9 g.) was heated under reflux for 1 hour with 2N-hydrochloric acid (100 c.c.), cooled, filtered, and washed well with water; in this way, 2-thio-1 : 3-dimethylhydantoin was obtained as colourless needles, m. p. 93° (Delépine, *loc. cit.*, gives m. p. 94·5°) (yield, 8·5 g., 94%).

The thiohydantoin (5 g.) in pyridine (10 c.c.) containing morpholine (4 g.) and benzaldehyde (3·5 g.) was heated under reflux for 1 hour; the solvent was partly removed and the mixture poured into 2N-hydrochloric acid (100 c.c.). On shaking, a granular solid was obtained which was collected and washed well with water, followed by a little methanol (yield, 7 g., 87%). *2-Thio-5-benzylidene-1 : 3-dimethylhydantoin* crystallised from acetone–ethanol as orange-red rhombs, m. p. 144° (Found: C, 62·5; H, 5·3; N, 12·1. $C_{13}H_{12}ON_2S$ requires C, 62·1; H, 5·2; N, 12·1%). 2-Thio-1 : 3-dimethylhydantoin (5 g.) in pyridine (10 c.c.) containing morpholine (4 g.) and acetone (10 c.c.) was heated under reflux for 1 hour. *2-Thio-1 : 3-dimethyl-5-isopropylidenehydantoin* (4·5 g., 72%) was isolated by the procedure described above and crystallised from methanol as orange needles, m. p. 118° (Found: C, 52·1; H, 6·5; N, 15·1. $C_8H_{12}ON_2S$ requires C, 52·2; H, 6·5; N, 15·2%). *n*-Butyraldehyde apparently condensed with the thiohydantoin under similar conditions, but the product was a gum which resisted crystallisation.

Reactions with Phenyl iso*Thiocyanate.*—Methylaminoacetonitrile (5 g.) in ether (10 c.c.) was added with cooling and stirring under nitrogen to phenyl *iso*thiocyanate (10 g.) in ether (15 c.c.). The gum which formed crystallised on scratching, and *5-amino-2-anilo-3-methylthiazole* (13 g., 89%) was obtained; it recrystallised from ethanol as orange needles, m. p. 140° (Found: C, 58·8; H, 5·7; N, 20·3. $C_{10}H_{11}N_3S$ requires C, 58·5; H, 5·4; N, 13·6%). When the condensation was repeated in ethyl acetate, the solution remained clear and addition of acetic anhydride (6 g.) yielded *5-acetamido-2-anilo-3-methylthiazole* (15 g., 85%). This recrystallised from ethanol as orange needles, m. p. 215° (Found: C, 58·4; H, 5·6. $C_{12}H_{13}ON_3S$ requires C, 58·3; H, 5·3%). The aminothiazole (10 g.) was heated under reflux for 1 hour with 2N-hydrochloric acid (100 c.c.), and the product collected and washed well with water. *2-Thio-3-phenyl-1-methylhydantoin* (9·5 g., 95%) recrystallised from ethanol as straw-coloured needles, m. p. 163° (Found: C, 58·5; H, 4·9; N, 13·8. $C_{10}H_{10}ON_2S$ requires C, 58·3; H, 4·9; N, 13·6%).

The thiohydantoin (5 g.) in pyridine (10 c.c.) containing morpholine (3 g.) and benzaldehyde (3 g.) was boiled under reflux for 1 hour, and the solution partly evaporated and shaken with 2N-hydrochloric acid (100 c.c.). The solid (6·5 g., 92%) obtained was washed with water, followed by a little methanol, and on recrystallisation from acetone–ethanol *2-thio-3-phenyl-5-benzylidene-1-methylhydantoin* was

obtained as pale yellow sheaves, m. p. 196° (Found: C, 69·8; H, 4·9; N, 9·5. $C_{17}H_{14}ON_2S$ requires C, 69·4; H, 4·8; N, 9·5%). The benzylidene compound (5 g.) was dissolved in acetic acid (10 c.c.) containing red phosphorus (3 g.) and heated under reflux for 24 hours. After cooling, filtration, and evaporation of the mixture to dryness *in vacuo*, addition of water (50 c.c.) gavea gum which was separated and crystallised from methanol. 2-*Thio*-3-*phenyl*-5-*benzyl*-1-*methylhydantoin* was obtained as colourless cubes, m. p. 133° (4 g., 80%) (Found: C, 69·2; H, 5·6; N, 9·2. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4; N, 9·5%). With a reflux period of 5 hours, a yield of 90% was obtained; use of dilute aqueous ammonia instead of water at the appropriate stage of the isolation removed most of the colour from the crude product. The benzylhydantoin (5 g.) in water (10 c.c.) and ethanol (10 c.c.) containing sodium hydroxide (4 g.) was heated under reflux for 24 hours; sulphuric acid (4·9 g., 1 equiv.) in water (10 c.c.) was added and the mixture evaporated to dryness. Extraction with hot methanol (4 × 100 c.c.) and evaporation of the solution gave a solid which, after washing with acetone and a little water, was pure β-phenyl-*N*-methylalanine (yield, 2·5 g., 82%).

In the same way, acetone (8 g.) was condensed with 2-thio-3-phenyl-1-methylhydantoin (5 g.) to give 2-*thio*-3-*phenyl*-1-*methyl*-5-iso*propylidenehydantoin* (4·5 g., 75%) which crystallised from methanol as orange rhombs, m. p. 152° (Found: C, 63·5; H, 5·8; N, 11·5. $C_{13}H_{14}ON_2S$ requires C, 63·4; H, 5·7; N, 11·4%). This was reduced with hydriodic acid and red phosphorus in acetic acid to 2-*thio*-3-*phenyl*-1-*methyl*-5-iso*propylhydantoin* (yield, 85%) which was obtained from methanol as colourless needles, m. p. 118—119° (Found: C, 63·0; H, 6·5; N, 11·3. $C_{13}H_{16}ON_2S$ requires C, 62·9; H, 6·5; N, 11·3%). Hydrolysis with aqueous alcoholic sodium hydroxide gave *N*-methylvaline (yield, 85%) which was isolated by the procedure described above. 2-Thio-3-phenyl-1-methylhydantoin (5 g.) and *n*-butyraldehyde (3 g.) in pyridine (10 c.c.) and morpholine (3 c.c.) were boiled under reflux for 1 hour. The solution was partly evaporated and shaken with 2N-hydrochloric acid (100 c.c.), whereupon a solid separated; this was washed with water and a little methanol. 2-*Thio*-3-*phenyl*-1-*methyl*-5-n-*butylidene*-*hydantoin* (yield, 4·5 g., 71%) was crystallised from methanol as pale yellow prisms, m. p. 123° (Found: C, 64·9; H, 6·4. $C_{14}H_{16}ON_2S$ requires C, 64·6; H, 6·2%).

*iso*Propylaminoacetonitrile (5 g.) in ether (10 c.c.) was added with cooling and stirring under nitrogen to phenyl *iso*thiocyanate (7 g.) in ether (15 c.c.). The solid (10 g., 85%) which crystallised from the solution was collected after 1 hour and washed with ether; 5-*amino*-2-*anilo*-3-iso*propylthiazole* recrystallised from ethanol as orange-red needles, m. p. 133° (Found: C, 61·8; H, 6·6; N, 18·4. $C_{12}H_{15}N_3S$ requires C, 61·8; H, 6·4; N, 18·0%). The aminothiazole (10 g.) was heated under reflux for 1 hour with 2N-hydrochloric acid (100 c.c.), and the product (9·5 g., 95%) collected and washed well with water, followed by a little ethanol. 2-*Thio*-3-*phenyl*-1-iso*propylhydantoin* recrystallised from ethanol as pale yellow needles, m. p. 198° (Found: C, 61·4; H, 6·2; N, 12·4. $C_{12}H_{14}ON_2S$ requires C, 61·6; H, 6·0; N, 12·0%).

The thiohydantoin (5 g.) was condensed with benzaldehyde (2·5 g.) in pyridine containing morpholine, and the product isolated in the usual way. 2-*Thio*-3-*phenyl*-5-*benzylidene*-1-iso*propylhydantoin* (6 g., 87%) was recrystallised from acetone–methanol as yellow needles, m. p. 174° (Found: C, 70·8; H, 5·9; N, 8·5. $C_{19}H_{18}ON_2S$ requires C, 70·8; H, 5·6; N, 8·7%). On reduction with hydriodic acid and red phosphorus in acetic acid, 2-*thio*-3-*phenyl*-5-*benzyl*-1-iso*propylhydantoin* (yield, 92%) was obtained, and this crystallised from methanol as colourless cubes, m. p. 133° (Found: C, 70·4; H, 6·4; N, 8·3. $C_{19}H_{20}ON_2S$ requires C, 70·4; H, 6·2; N, 8·6%). The benzylhydantoin (5 g.) was hydrolysed by boiling it under reflux for 24 hours with sodium hydroxide (4 g.) in water (10 c.c.) and ethanol (10 c.c.); neutralisation with sulphuric acid (1 equivalent) and evaporation to dryness, followed by extraction with hot methanol (5 × 100 c.c.), gave crude β-*phenyl*-N-iso*propylalanine* which was purified by washing it with acetone, followed by water (yield, 2·7 g., 83%). The amino-acid sublimed without melting and was only sparingly soluble in methanol or water; it recrystallised from a large volume of the latter as colourless plates (Found: N, 6·8. $C_{12}H_{17}O_2N$ requires N, 6·8%).

2-Thio-3-phenyl-1-*iso*propylhydantoin (5 g.) was condensed with *n*-butyraldehyde (2·5 g). in pyridine and morpholine, and the mixture shaken with 2N-hydrochloric acid (100 c.c.). The product was obtained as an oil but it crystallised from methanol as pale yellow needles, m. p. 124° (4·5 g., 70%), of 2-*thio*-3-*phenyl*-1-iso*propyl*-5-n-*butylidenehydantoin* (Found: C, 66·6; H, 7·2; N, 9·7. $C_{16}H_{20}ON_2S$ requires C, 66·7; H, 6·9; N, 9·7%). This was reduced with hydriodic acid and red phosphorus in acetic acid to 2-*thio*-3-*phenyl*-1-iso*propyl*-5-n-*butylhydantoin* (yield, 89%) which crystallised from light petroleum as colourless needles, m. p. 63° (Found: C, 66·4; H, 7·8; N, 9·6. $C_{16}H_{22}ON_2S$ requires C, 66·2; H, 7·6; N, 9·7%). Alkaline hydrolysis and isolation as above gave N-iso*propylnorleucine* (90%) which sublimed without melting and was crystallised from aqueous methanol as colourless prisms (Found: N, 8·0. $C_9H_{19}O_2N$ requires N, 8·1%). 2-Thio-3-phenyl-1-*iso*propylhydantoin (5 g.) was heated under reflux for 24 hours with acetone (10 c.c.) in pyridine (10 c.c.) containing morpholine (3 g.). On isolation of the product, it was found to contain only starting material. 2-Thio-3-phenyl-1-methylhydantoin (5 g.) was heated under reflux for 24 hours with acetone (10 c.c.) in acetic acid (10 c.c.) containing fused sodium acetate (5 g.); the starting material was isolated unchanged. 2-Thio-3-phenyl-1-methylhydantoin (5 g.) was heated under reflux for 2 hours with benzaldehyde (3 g.) in acetic acid (10 c.c.) containing fused sodium acetate (5 g.); on pouring the mixture into water (100 c.c.) and washing of the product with ethanol, 2-thio-3-phenyl-5-benzylidene-1-methylhydantoin (6 g.) was obtained.

3-Phenyl-1-methylhydantoin (Delepine, *loc. cit.*) (5 g.) and benzaldehyde (3 g.) in pyridine (10 c.c.) and morpholine (3 g.) were heated under reflux for 10 hours, and the product was distilled in steam until the distillate was free from solvent or benzaldehyde; the residue contained only unchanged hydantoin. Acetone failed to condense with the hydantoin under similar conditions.

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497. 2 : 5-*Diketomorpholines, Their Synthesis and Stability.*

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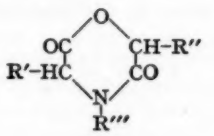
Various substituted α′-bromoacyl-α-amino-acids and the corresponding hydroxy-amino-acids (*e.g.*, I) have been prepared and shown to yield lactones (II) with varying ease depending on substitution and steric configuration. These effects are ascribed to electronic influences of the substituents on lactonisation and to steric hindrance respectively. Biological results with some of the lactones described are appended.

It was reported (Cook, Cox, and Farmer, this vol., p. 1022; *Nature*, 1948, **162**, 61) that lateritiin, an antibiotic produced by *F. lateritium*, was converted by treatment with sodium hydroxide into a hydroxy-acid (I) which lactonised spontaneously to form (II; R′ = R″ = Pr^i, R‴ = Me). The present work was concerned with factors influencing the formation of this practically unknown diketomorpholine ring system, and with the effect of various alkyl groups on some of its properties. The lactones which were prepared were also examined for possible

$Pr^i{\cdot}CH(OH){\cdot}CO{\cdot}NMe{\cdot}CHPr^i{\cdot}CO_2H$
(I.)


(II.)

antibacterial activity, in the hope of throwing some light on the mode of action of lateritiin. The latter is chemically unreactive and it has been suggested that its biological properties might be due to one or other of its breakdown products. The activity was not shown by the natural lactone but it was possible that the solubility or stability of the latter might have been unfavourable for penetration of the bacterial cell, and the considerable variation in these two properties in the synthetic lactones appeared to justify their examination.

Chadwick and Pascu (*J. Amer. Chem. Soc.*, 1943, **65**, 392) during the attempted resolution of *N*-α-bromopropionylglycine found that salts of this compound deteriorated on being kept and, by heating the sodium salt *in vacuo*, were able to isolate a compound which they formulated as 3 : 6-diketo-2-methylmorpholine (II; R′ = R‴ = H, R″ = Me). When this procedure was repeated using *N*-α-bromo*iso*valerylglycine, 3 : 6-*diketo*-2-iso*propylmorpholine* (II; R′ = R‴ = H, R″ = Pr^i) sublimed from the reaction mixture. This compound was soluble in hot water, in which it hydrolysed rapidly giving, on evaporation, N-α-*hydroxy*iso*valerylglycine* which could be sublimed in a high vacuum without change. In the same way, the sodium salt of *N*-α-bromo*iso*valerylsarcosine yielded 3 : 6-*diketo*-4-*methyl*-2-iso*propylmorpholine* (II; R′ = H, R″ = Pr^i, R‴ = Me), a water-soluble product which hydrolysed when warmed in aqueous solution. *N*-α-Hydroxy*iso*valerylsarcosine was obtained in this way as an oil which lost its acidic properties on being kept for 5 days at 20° or on distillation in a high vacuum, by reverting into the lactone. This reacted readily with alcoholic ammonia to give *N*-α-*hydroxy*iso*valerylsarcosine amide*.

The bromoacylamino-acids used in this preliminary work were prepared by the method of Fischer and Schenkel (*Annalen*, 1907, **354**, 13) which involved treating a salt of the amino-acid with an acid chloride in ice-cold aqueous solution in the presence of excess of alkali. This procedure was unsatisfactory with the more complex *N*-alkylamino-acids, as condensation was slow with the result that considerable hydrolysis of the acid chloride occurred at the same time. It was found convenient to shake the acid chloride with two equivalents of amino-acid suspended in dry chloroform whereupon a good yield of the desired product was obtained, and this procedure was used in all subsequent preparations. N-*Chloroacetyl*-N-*methylvaline*, obtained in this way, was converted into 2 : 5-*diketo*-4-*methyl*-3-iso*propylmorpholine* (II; R′ = Pr^i, R″ = H, R‴ = Me) by heating its sodium salt in a high vacuum. This was quickly hydrolysed, on heating it in aqueous solution, to *N*-hydroxyacetyl-*N*-methylvaline from which it was recovered after several weeks at room temperature or on distillation in a high vacuum.

None of the compounds prepared so far contained more than one asymmetric centre but the next product had two asymmetric centres and so existed as two diastereoisomers. Crude N-α-*bromo*iso*valeryl*-N-*methylvaline* was obtained from the condensation as an oil which decomposed on attempted distillation in a high vacuum. It was purified by dissolving it in sodium carbonate solution whereupon a small amount of neutral material was removed, and on acidification the bromo-acid was recovered as a colourless oil which partly crystallised after several

weeks. Repeated recrystallisation gave a pure material which was almost certainly one of the two diastereoisomers, but for the preparation of the corresponding hydroxy-acid the crude condensation product was used. This was heated under reflux with aqueous pyridine for several hours and a product was obtained which was already partly lactonised. The neutral material, which amounted to approximately 50% of the whole, was separated and heated under reflux in aqueous methanol for a further 5 hours whereupon hydrolysis occurred only to the extent of 20%; the unhydrolysed material was isolated as an oil which crystallised on being kept and recrystallisation gave 2 : 5-diketo-4-methyl-3 : 6-di*iso*propylmorpholine (II; R′ = R″ = Pr^{i}, R‴ = Me), m. p. 82°, which proved to be identical with the DL-LD-form of this compound obtained previously (Cook, Cox, and Farmer, *loc. cit.*). The acidic material obtained in the pyridine hydrolysis lactonised slowly and the lactone formed was largely the other (DD-LL) diastereoisomer as on being heated under reflux in aqueous methanol for 5 hours it was reconverted almost completely into the hydroxy-acid. This behaviour may be explained in terms of the steric configurations of the two forms of the molecule. The DL-LD-lactone has, in consequence of its definition, the configuration in which the two *iso*propyl groups are on opposite sides of the plane of the morpholine ring and in aqueous solution an equilibrium involving hydrolysis and lactonisation is established favouring the latter. The DD-LL-form of the lactone appears to be sterically hindered so that, although hydrolysis of the two forms takes place at comparable rates, lactonisation of the DD-LL-form is much slower and the equilibrium in aqueous solution favours the hydroxy-acid. It was of some interest incidentally to see whether the *amide* of N-α-*hydroxy*isov*aleryl*-N-*methylvaline* could be cyclised as easily as the free acid; the amide was prepared by the action of alcoholic ammonia on the DL-LD-diastereoisomer of the lactone but sublimed unchanged in a high vacuum.

*N-iso*Propylvaline condensed with chloracetyl chloride to form N-*chloracetyl*-N-iso*propyl-valine* which on being kept in sodium carbonate solution was converted into 2 : 5-*diketo*-3 : 4-*di*-iso*propylmorpholine* (II; R′ = R‴ = Pr^{i}, R″ = H) which hydrolysed only slowly on being heated under reflux in aqueous methanol. Crude N-α-*bromo*isov*aleryl*-N-iso*propylvaline* was prepared in the usual way but, when an attempt was made to purify it by solution in dilute sodium carbonate, approximately 50% of the material lactonised within 5 minutes to form DL-LD-2 : 5-*diketo*-3 : 4 : 6-*tri*iso*propylmorpholine* (II; R′ = R″ = R‴ = Pr^{i}) whilst the remainder was unaffected after a further hour in the alkaline solution. This difference between the two diastereoisomers must be attributed to the steric factor already discussed. The DL-LD-lactone was unaffected by boiling aqueous methanol but was hydrolysed on being left with aqueous alcoholic sodium hydroxide and the hydroxy-acid which was formed lost its acidic properties after 24 hours at 20°.

The results given above suggested that addition of alkyl groups to the diketomorpholine ring system increased its stability and also the ease of its formation, but did not indicate the way in which this effect was operating. It was therefore decided to study the result of further small variarions in structure, and lactonisation of the bromoacylamino-acids in sodium carbonate solution was selected as the most suitable reaction for investigation. It was necessary to use the crude bromo-acids obtained from the condensations as any attempt to recrystallise these would almost certainly have resulted in a partial separation of the two diastereoisomers. This crude material contained a neutral product formed during the condensation; in the case of the *N*-methylamino-acids, it was possible to remove this at the beginning of the reaction, but with the *N-iso*propylamino-acids lactonisation was too rapid for this to be done. This neutral material consisted partly of a substance which decomposed on attempted distillation in a high vacuum but it also contained some of the lactone which must have been formed by the reaction of the bromacylamino-acid with the excess of amino-acid present during the early stages of the condensation.

The results obtained in these experiments are set out in Table I in which the percentages are computed from the amounts isolated by simple extraction with ether. No claim is made that they provide information of the exactitude obtained in kinetic studies but it is nevertheless possible to reach a number of conclusions about the course of the reaction. It may be assumed that the lactonisation is an internal S_N2 reaction; if it were an S_N1 reaction with ionisation of the bromine as the rate-controlling step, this process would presumably be independent of the steric configuration of the molecule and the diastereoisomer in which lactonisation is sterically hindered should be converted into the corresponding hydroxy-acid whereas in fact the material which is not lactonised is recovered unchanged. Viewed as an S_N2 reaction, the process should involve inversion at the carbon atom concerned and, although no optically active compound has been studied in sodium carbonate solution, it has been shown (Cook, Cox, and Farmer, *loc. cit.*)

TABLE I.

Lactonisation of α-bromoacylamino-acids in two equivalents of N-*sodium carbonate solution at* 20°.

	* Lactone formed after 5 mins.	Additional lactone formed after 1 hr.	Residual acid.
N-α-Bromo-*n*-butyryl-*N*-methylvaline	15%	21%	53%
N-α-Bromo-*n*-valeryl-*N*-methylvaline	13	15	59
N-α-Bromo*iso*valeryl-*N*-methylvaline	10	6	74
N-α-Bromo-*n*-butyryl-*N*-methylnorvaline	7	11	74
N-α-Bromo-*n*-valeryl-*N*-methylnorvaline	4	9	82
N-α-Bromo*iso*valeryl-*N*-methylnorvaline	2	3	89
N-α-Bromo-*n*-butyryl-*N*-*iso*propylvaline	57	—	34
N-α-Bromo-*n*-valeryl-*N*-*iso*propylvaline.....	63	—	29
N-α-Bromo*iso*valeryl-*N*-*iso*propylvaline	53	—	39
N-α-Bromo-*n*-butyryl-*N*-*iso*propylnorvaline	53	—	40
N-α-Bromo-*n*-valeryl-*N*-*iso*propylnorvaline	57	—	36
N-α-Bromo*iso*valeryl-*N*-*iso*propylnorvaline	54	—	42

* Includes neutral impurity in starting material.

that in the similar process of heating L-α-bromo*iso*valeryl-*N*-methyl-DL-valine with pyridine and water, replacement of the bromine atom occurs with inversion and without appreciable racemisation. In this process, the bromo-acid is subject to two competing reactions, hydrolysis to *N*-α-hydroxy*iso*valeryl-*N*-methylvaline and direct lactonisation; moreover, the two products are also subject to interconversion (see above). It must therefore be concluded that removal of the bromine atom by both of these processes is accompanied by inversion and that the lactonisation of the hydroxy-acid and hydrolysis of the lactone are characterised by retention of configuration. Addition of alkyl substituents to the bromoacylamino-acid appears to affect the lactonisation in two ways; first there is an acceleration due to their electron-releasing properties which aids the separation of the bromine ion, and secondly a retardation due to steric hindrance. In the case of one diastereoisomer, the steric effect is overwhelmingly predominant but with the other, the net effect is governed by the position of the alkyl group concerned. In the amino-acid portion of the molecule, the electronic effect is more important so that valine derivatives lactonise faster than norvaline compounds, and substituted *N*-*iso*propyl-amino-acids lactonise faster that substituted *N*-methylamino-acids. In the case of the alkyl group attached to the carbon atom carrying the bromine atom, however, the steric effect becomes more important. This is easy to understand when it is remembered that an S_N2 reaction involves a transition state with five groups in the vicinity of the carbon atom under attack so that bulky constituents must be expected to cause some retardation.

As the lactonisation of the α′-hydroxyacyl-α-amino-acids involves retention of optical configuration, it must take place by a mechanism different from that discussed above. It seems unprofitable to speculate on the mechanism of this process without further experimental evidence.

Several of the lactones prepared during this work were examined for antibacterial activity in the Experimental Medicine Unit of Glaxo Laboratories Ltd. whom we thank for these facilities. Examined by the method of serial dilution in broth or serum-broth they inhibited the growth of *Staph. aureus* and *Esch. coli* only slightly even at a concentration of 1/100. *Esch. coli*, *Staph. aureus*, *B. adherans*, and *Bact. typhi* were not inhibited when streaked across agar plates prepared with the lactones in a concentration of 1/500; haemolytic *Strep.* and *Strep. pneumoniæ* were inhibited by the lactones in similar concentration on blood-agar plates. Clearly the lactones show none of the biological activity of lateritiin.

EXPERIMENTAL.

Reactions with Glycine.—*N*-α-Bromo*iso*valerylglycine (Fischer and Schenkel, *loc. cit.*) (5 g.) was dissolved in 2N-sodium hydroxide (10·5 c.c.) and evaporated to dryness *in vacuo*; the sodium salt obtained in this way was heated at 200° and 10^{-5} mm. whereupon 3 : 6-*diketo*-2-iso*propylmorpholine* (2 g.; 60%) slowly sublimed out of the reaction. It recrystallised from chloroform as colourless needles, m. p. 150° (Found: C, 53·6; H, 7·2; N, 8·9. $C_7H_{11}O_3N$ requires C, 53·5; H, 7·0; N, 8·9%). This product (1 g.) was heated in water (3 c.c.) on the steam-bath for 30 minutes and evaporated *in vacuo*; the residue was N-α-*hydroxyisovalerylglycine* (1·1 g.) which crystallised from water as colourless prisms, m. p. 160° (Found: C, 48·2; H, 7·4; N, 7·8. $C_7H_{13}O_4N$ requires C, 48·0; H, 7·4; N, 8·0%).

Reactions with Sarcosine.—*N*-α-Bromo*iso*valerylsarcosine (Levene, Simms, and Pfaltz, *J. Biol. Chem.*, 1926, **70**, 262) (5 g.) was dissolved in 2N-sodium hydroxide (10 c.c.) and evaporated to dryness *in vacuo*; when the residue was heated at 150° and 10^{-5} mm., 3 : 6-*diketo*-4-*methyl*-2-iso*propylmorpholine* (2·5 g., 73%) distilled from the reaction as an oil which crystallised on cooling to give colourless prisms,

m. p. 49—51° (Found : N, 8·1. $C_8H_{13}O_3N$ requires N, 8·2%). The lactone (1 g.) was heated in water (3 c.c.) on the steam-bath for 30 minutes and then diluted with ether (100 c.c.). After drying ($MgSO_4$) for 30 minutes, the solvent was removed *in vacuo* leaving an acid oil which reverted to the lactone during 5 days at 20° in an open flask. The lactone (1 g.) in methanol (10 c.c.) was added to liquid ammonia (5 c.c.) and left at 0° for 16 hours. Evaporation gave N-*α-hydroxyisovalerylsarcosine amide* (1·1 g.) which crystallised from methanol as colourless cubes, m. p. 139° (Found : C, 51·1; H, 8·8; N, 14·5. $C_8H_{16}O_3N_2$ requires C, 51·1; H, 8·5; N, 14·9%).

Reactions with N-*Methylvaline.*—*N*-Methylvaline (8 g.) was suspended in dry chloroform (40 c.c.) cooled in ice, and chloroacetyl chloride (3·4 g.) was added. The mixture was shaken for 1 hour during which the temperature was allowed to rise to 20°. Most of the chloroform was then removed *in vacuo* and the residue was extracted with ether (100 c.c.) and water (20 c.c.). The ether layer was washed with water (10 c.c.), dried, and evaporated to give N-*chloroacetyl*-N-*methylvaline* as a gum which crystallised from benzene as colourless flakes, m. p. 112° (yield : 4·4 g., 70%) (Found : C, 46·2; H, 6·5; N, 6·5. $C_8H_{14}O_3NCl$ requires C, 46·3; H, 6·8; N, 6·8%). This product (3 g.) was dissolved in 2N-sodium hydroxide (7·5 c.c.) and evaporated to dryness *in vacuo*; when heated at 120° and 10^{-5} mm., 2 : 5-*diketo*-4-*methyl*-3-iso*propylmorpholine* (1·8 g.; 72%) distilled as a colourless oil (Found : N, 8·1. $C_8H_{13}O_3N$ requires N, 8·2%). The lactone (1 g.) was dissolved in water (3 c.c.) and heated on the steam-bath for 30 minutes; it was then diluted with ether (100 c.c.), dried ($MgSO_4$) for 30 minutes, and evaporated *in vacuo*. *N*-Hydroxyacetyl-*N*-methylvaline was obtained as a gum which lactonised on distillation in a high vacuum or after several weeks in an open flask at 20°.

N-Methylvaline (8 g.) was suspended in dry chloroform (40 c.c.) cooled in ice, and α-bromo*iso*valeryl chloride (6·1 g.) was added. The mixture was shaken for 1 hour during which the temperature was slowly allowed to rise to 20° and then the chloroform was removed *in vacuo*. Ether (100 c.c.) and water (20 c.c.) were added and after the mixture had been well shaken the ether layer was extracted with N-sodium carbonate (50 c.c.) and washed with water (10 c.c.). The combined alkaline solution was immediately acidified and re-extracted with ether (2 × 50 c.c.) evaporation of the solvent *in vacuo* gave a colourless oil (7·2 g., 80%). After several weeks, crystallisation took place and several recrystallisations from benzene–light petroleum gave N-*α-bromoisovaleryl*-N-*methylvaline* as colourless flakes, m. p. 120° (Found : C, 45·0; H, 7·0; N, 4·5. $C_{11}H_{20}O_3NBr$ requires C, 44·9; H, 6·8; N, 4·8%). Crude *N*-α-bromo*iso*valeryl-*N*-methylvaline (8 g.) was heated under reflux with pyridine (15 c.c.) and water (20 c.c.) for 2 hours and the solution was concentrated by evaporation until most of the pyridine was removed. Ether (100 c.c.) and 2N-hydrochloric acid (20 c.c.) were added and, after the solution had been shaken, the ether layer was extracted with N-sodium carbonate (30 c.c.) followed by water (10 c.c.). The oil (2·5 g.), obtained on evaporation of the ether, was heated under reflux in methanol (10 c.c.) and water (10 c.c.) for 5 hours, and 2·3 g. of neutral material were recovered (a similar result was obtained when another sample was heated under reflux for 15 hours). This crystallised on being kept, and recrystallisation from light petroleum gave colourless cubes, m. p. 82°, which proved to be identical with the DL-LD-diastereoisomer of 2 : 5-diketo-4-methyl-3 : 6-di*iso*propylmorpholine obtained previously (Cook, Cox, and Farmer, *loc. cit.*). The sodium carbonate solution and washings were acidified and extracted with ether (2 × 100 c.c.); evaporation gave a colourless gum (2·6 g.). After 2 weeks at 20° in an open flask, this yielded 1·4 g. of neutral oil which when heated under reflux for 5 hours in aqueous methanol was hydrolysed to the extent of 90%.

DL-LD-2 : 5-Diketo-4-methyl-3 : 6-di*iso*propylmorpholine (2 g.) in methanol (15 c.c.) was added to liquid ammonia (10 c.c.) and left at 0° for 16 hours. Evaporation gave N-*α-hydroxyisovaleryl*-N-*methylvaline amide* (2·1 g.) which crystallised from benzene–light petroleum as colourless prisms, m. p. 120° (Found : N, 12·0. $C_{11}H_{22}O_3N_2$ requires N, 12·2%).

Reactions with N-iso*Propylvaline.*—Chloroacetyl chloride (3·5 g.) was added to *N-iso*propylvaline (10 g.) in dry chlorform (50 c.c.) and after the solution had been shaken for 1 hour the product was isolated as in the preparation of *N*-chloroacetyl-*N*-methylvaline. Recrystallisation from benzene gave N-*chloroacetyl*-N-iso*propylvaline* (6 g., 83%) as colourless prisms, m. p. 105° (Found : C, 51·3; H, 7·7; N, 6·0. $C_{10}H_{18}O_3NCl$ requires C, 51·0; H, 7·6; N, 5·9%). When this acid (2 g.) was dissolved in N-sodium carbonate (20 c.c.) and left at 20° for 1 hour, separation of the acidic and neutral products yielded unchanged starting material (1 g.) and 2 : 5-*diketo*-3 : 4-di*isopropylmorpholine* (0·75 g., 44%). This distilled at 100°/10^{-5} mm. and crystallised on being kept to form colourless prisms, m. p. 53° (Found : N, 7·0. $C_{10}H_{17}O_3N$ requires N, 7·0%).

*N-iso*Propylvaline (10 g.) in dry chloroform (50 c.c.) was cooled in ice and shaken with α-bromo*iso*-valeryl chloride (6·2 g.) for 1 hour, the temperature being allowed to rise slowly to 20°. Most of the chloroform was then removed *in vacuo*, and ether (100 c.c.) and water (20 c.c.) were added. The ether layer was shaken with N-sodium carbonate (50 c.c.) for 5 minutes and washed with water (10 c.c.), the sodium carbonate solution and washings being acidified and extracted with ether. The acidic product was DD-LL-N-*α-bromoisovaleryl*-N-iso*propylvaline* (3·2 g., 39%) which crystallised from light petroleum as colourless prisms, m. p. 126° (Found : C, 48·9; H, 7·7; N, 4·4. $C_{13}H_{24}O_3NBr$ requires C, 48·4; H, 7·5; N, 4·3%). The neutral product (3·2 g., 53%) distilled at 100°/10^{-5} mm. with partial decomposition but redistilled smoothly to give DL-LD-2 : 5-*diketo*-3 : 4 : 6-*tri*iso*propylmorpholine* as colourless prisms, m. p. 48—50° (Found : N, 5·9. $C_{13}H_{23}O_3N$ requires N, 5·8%).

Lactonisation in Sodium Carbonate Solution.—The bromo-acids were prepared by the condensation of the appropriate acid chloride and amino-acid in dry chloroform, using the procedure described above. After removal of the chloroform *in vacuo*, ether and water were added and the ether layer was shaken for 5 minutes with N-sodium carbonate solution (2 equivalents) and washed with a little water. After a further hour, the aqueous solution was re-extracted with ether, and the bromo-acid recovered by acidification. The lactone obtained in this way from *N*-α-bromo*iso*valeryl-*N*-methylvaline was substantially the DL-LD-diastereoisomer and it seems likely that all the products obtained in this way are the DL-LD-forms. The bromo-*N-iso*-propylamino-acids could be purified without difficulty but the bromo-*N*-methyl-amino-acids crystallised only after being left for several weeks. The products prepared in this way are listed in Table II.

TABLE II.

Bromo-acid.	M. p.	Found, N, %.	Reqd. N, %.	Corresponding lactone. M. p.	Found, N, %.	Reqd. N, %.
N-α-*Bromo*-n-*butyryl*-N-*methylvaline*	99—100°	4·9	5·0	40°	7·2	7·0
N-α-*Bromo*-n-*valeryl*-N-*methylvaline*	oil	—	—	oil	6·5	6·6
N-α-*Bromo*-n-*butyryl*-N-*methylnorvaline*	105	4·8	5·0	61	7·2	7·0
N-α-*Bromo*-n-*valeryl*-N-*methylnorvaline*	77	4·6	4·8	78	6·7	6·6
N-α-*Bromoisovaleryl*-N-*methylnorvaline*	122	4·9	4·8	45	6·8	6·6
N-α-*Bromo*-n-*butyryl*-N-iso*propylvaline*	112	4·3	4·5	43—45	6·1	6·2
N-α-*Bromo*-n-*valeryl*-N-iso*propylvaline*	96	4·0	4·3	45—46	5·7	5·8
N-α-*Bromo*-n-*butyryl*-N-iso*propylnorvaline* ...	110—112	4·4	4·5	68	6·2	6·2
N-α-*Bromo*-n-*valeryl*-N-iso*propylnorvaline* ...	107	4·2	4·3	36—38	5·9	5·8
N-α-*Bromoisovaleryl*-N-iso*propylnorvaline* ...	117	4·3	4·3	oil	5·7	5·8

Grateful acknowledgment is made of the award of an Australian National University Scholarship (to S. F. C.) which made participation in this work possible. We also thank Sir Ian Heilbron, D.S.O., F.R.S., for his interest and encouragement.

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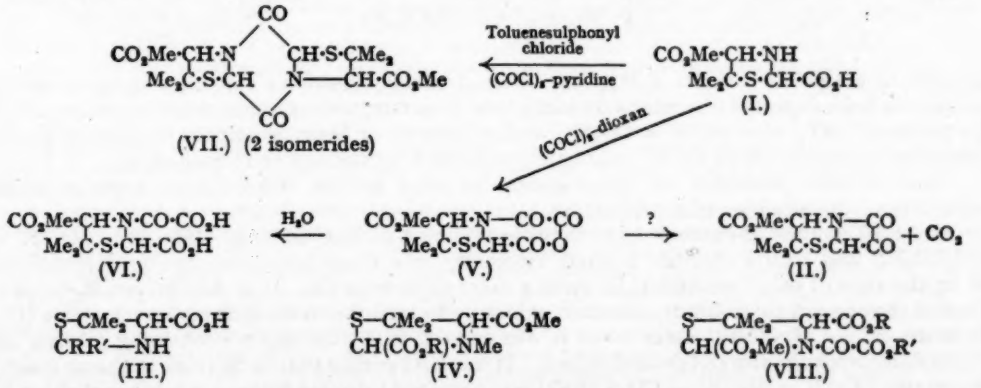
498. *Syntheses in the Penicillin Field. Part I. The Reactions between Oxalyl Chloride and Certain Thiazolidines.**

By R. BENTLEY, A. H. COOK, J. A. ELVIDGE, and G. SHAW.

Various thiazolidines bearing a free NH-group and a carboxyl group in the 2- or the 4-position were treated with oxalyl chloride in pyridine or in dioxan. Under the latter conditions *anhydrides* of *carboxy*-3-*oxalothiazolidines* formed the main products; with appropriate reagents these afforded 3-*oxalo*- or 3-*alkoxalyl*-*thiazolidines*, representatives of which were independently synthesised. In pyridine the major reaction was one of dehydration to complex *diketopiperazines* which in several instances were isomeric with *diketopiperazines* obtained with other acid chlorides. Similar thiazolidines lacking a free 2- or 4-carboxyl group afforded only 3-*oxalothiazolidines* and *oxalylbis*-3-*thiazolidines*.

IT was observed that interaction of 4-*carbomethoxy*-5 : 5-*dimethylthiazolidine*-2-*carboxylic acid* (I) and oxalyl chloride under mild conditions led to evolution of carbon dioxide, and in view of supporting observations this reaction was examined more closely in the hope that it might be associated with the formation of the keto-β-lactam (II) which would be a desirable intermediate for the ultimate synthesis of penicillins. The apparent simplicity of this reaction soon proved, however, to be deceptive and the present paper records the results of a more systematic examination of the interaction of oxalyl chloride with various thiazolidines as a preliminary to investigating more labile products.

Endeavours were first made to obtain (I) by esterification of the more easily accessible 2-carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylic acid (III; R = H, R′ = CO_2Me)

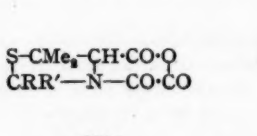


* A very small part of the work described in this Series was carried out during the war-time Anglo-American co-operative research project on penicillin. None of the present work, however, is described in "The Chemistry of Penicillin," Princeton Univ. Press, 1949.

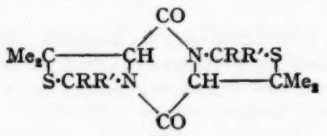
(see below), followed by half-hydrolysis. Treatment of (III; R = H, R′ = CO_2Me) with diazomethane, however, gave mainly dimethyl 3 : 5 : 5-trimethylthiazolidine-2 : 4-dicarboxylate (IV; R = Me) (*hydrochloride*) which was hydrolysed to 4-*carbomethoxy*-3 : 5 : 5-*trimethylthiazolidine*-2-*carboxylic acid* (IV; R = H) (*benzylamine* salt); this formulation is justified by the half-hydrolysis of the analogous compound lacking the *N*-Me group which afforded the 2-carboxy-derivative. (I) was eventually prepared (*a*) by interaction of penicillamine methyl ester and potassium glyoxylate, and more practicably (*b*) by a similar interaction with methyl dimethoxyacetate to give *dimethyl* 5 : 5-*dimethylthiazolidine*-2 : 4-*dicarboxylate* (*hydrochloride*), followed by half-hydrolysis to (I) [identified with the product of (*a*)] which was conveniently isolated as its *benzylamine* salt.

(I) reacted with oxalyl chloride in dioxan to give the *oxalo-carboxylic anhydride* (V) which with water afforded the *oxalo-carboxylic acid* (VI). In pyridine with oxalyl chloride, (I) afforded a product of unelucidated structure which was at one time (erroneously) thought to be (II), but the main product was a dimeric anhydride, *i.e.*, a *diketopiperazine* (VII). It had been very early observed in these laboratories that toluene-*p*-sulphonyl chloride, among other acid halides, readily converted thiazolidine-4-carboxylic acids into complex diketopiperazines so that the formation of (VII) at first occasioned no surprise. However, although a diketopiperazine was formed when (I) was treated with toluene-*p*-sulphonyl chloride, it was isomeric, presumably stereoisomeric, with the earlier material. Stereoisomeric forms of (VII) are theoretically possible, and the isolation of other pairs of isomerides of this kind suggests that the identity of the acid chloride may be important generally in deciding the steric configuration of the anhydride.

2-*Carbomethoxy*-5 : 5-*dimethylthiazolidine*-4-*carboxylic acid* (III; R = H, R′ = CO_2Me), obtained from penicillamine and methyl dimethoxyacetate, reacted with ethoxalyl chloride in chloroform–pyridine to give 2-*carbomethoxy*-3-*ethoxalyl*-5 : 5-*dimethylthiazolidine*-4-*carboxylic acid* (VIII; R = H, R′ = Et), whereas with oxalyl chloride in dioxan the *oxalo-carboxylic anhydride* (IX; R = H, R′ = CO_2Me) was obtained. The latter reacted with ethanol to give exclusively the *ethoxalyl-carboxylic acid* (VIII; R = H, R′ = Et) [converted into the mixed *ester* (VIII; R = Me, R′ = Et) by diazomethane], and with water to give the 3-*oxalo-carboxylic acid* (VIII; R = R′ = H) isolated as its *dibenzylamine* salt. Interaction of (III; R = H, R′ = CO_2Me) with oxalyl chloride in pyridine alone was vigorous and a small quantity of a



(IX.)



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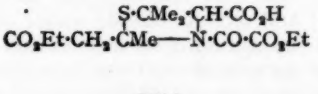

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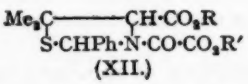

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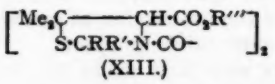

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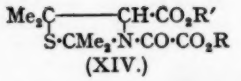

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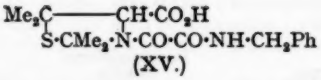

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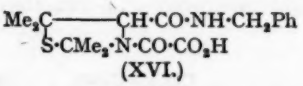

(XVI.)

product of empirical formula $C_9H_{11}O_4NS$ was obtained; however this showed none of the properties to be expected of a relatively labile keto-β-lactam, and its nature remains unelucidated. In pyridine, (III; R = H, R′ = CO_2Me) and toluene-*p*- or benzene-sulphonyl chloride gave a *diketopiperazine* (X; R = H, R′ = CO_2Me), possibly a mixture of stereoisomerides.

These results prompted an investigation of some further thiazolidines, some of which offered fewer possibilities of complication.

2 : 5 : 5-Trimethyl-2-carbethoxymethylthiazolidine-4-carboxylic acid (III; R = Me, R′ = CH_2CO_2Et) and oxalyl chloride reacted vigorously, the thiazolidine undergoing dehydration, as in the case of other examples, to yield a *diketopiperazine* (X; R = Me, R′ = $CH_2{\cdot}CO_2Et$). Part of the original thiazolidine, however, evidently formed the oxalo-carboxylic anhydride (IX; R = Me, R′ = $CH_2{\cdot}CO_2Et$) since when it was treated with chloroform containing ethanol the crystalline *carboxylic acid* (XI) was obtained. It was noteworthy that in this case the same diketopiperazine (X; R = Me, R′ = $CH_2{\cdot}CO_2Et$) was obtained by using toluene-*p*-sulphonyl chloride.

2-Phenyl-5 : 5-dimethylthiazolidine-4-carboxylic acid (III; R = H, R′ = Ph) and oxalyl chloride in dioxan gave the *anhydride* (IX; R = H, R′ = Ph), affording with ethanol the

ethoxalyl-acid (XII; R = H, R′ = Et), the structure of which was confirmed as in an earlier case by direct preparation. The compound (XII; R = H, R′ = Et) obtained from the the anhydride and ethanol was accompanied by an *isomeride* which is almost certainly represented by (XII; R = Et, R′ = H), the alternative product of ring-scission. Treatment of the parent thiazolidine with oxalyl chloride in pyridine, on the other hand, gave one form of the *diketopiperazine* (X; R = H, R′ = Ph) together with the *oxalyl-dicarboxylic acid* (XIII; R = H, R′ = Ph, R″ = H). The latter was esterified to give one form of the *diester* (XIII; R = H, R′ = Ph, R″ = Me), two other forms resulting from the condensation of *methyl 2-phenyl-5 : 5-dimethylthiazolidine-4-carboxylate* with oxalyl chloride in dioxan. It was of interest to find that the foregoing diketopiperazine (X; R = H, R′ = Ph) isomerised in a boiling mixture of hydrochloric and acetic acids and that the resulting *isomeride* was identical with the diketopiperazine formed from the parent thiazolidine (III; R = H, R′ = Ph) and toluene-*p*-sulphonyl chloride.

2 : 2 : 5 : 5-Tetramethylthiazolidine-4-carboxylic acid (III; R = R′ = Me) with oxalyl chloride in dioxan afforded the *anhydride* (IX; R = R′ = Me) and thence the 3-*ethoxalyl*-, the 3-*methoxalyl*-, and the 3-*oxalo-thiazolidine* (XIV) (R = Et, Me, and H, respectively; R′ = H), the last two compounds giving rise to the same *dimethyl* ester (XIV; R = R′ = Me). With ethoxalyl chloride in chloroform–pyridine, 2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid gave (XIV; R = Et, R′ = H) directly, from which the 3-N-*benzyloxamyl* derivative (XV) was prepared. The compound (XV) was also obtained by treating the anhydride (IX; R = R′ = Me) with benzylamine, though when the reaction was performed in dioxan a second *benzylamide* was formed to which structure (XVI) is assigned, stereoisomerism being impossible. By contrast with the reaction in dioxan, 2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid reacted in pyridine with oxalyl chloride to yield a *diketopiperazine* (X; R = R′ = Me), isomeric with one obtained by use of toluene-*p*-sulphonyl chloride (Cook, Elvidge, Hall, Heilbron, and Shaw, *CPS*, 270; "The Chemistry of Penicillin," Princeton Univ. Press, 1949, pp. 967—968). The ester, methyl 2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylate, with oxalyl chloride in dioxan gave, as might have been expected, the *oxalylbis-3-thiazolidine* (XIII; R = R′ = R″ = Me) together with the 3-*oxalo-carboxylate* (XIV; R = H, R′ = Me) which was converted into the *diester* (XIV; R = R′ = Me) by diazomethane.

Experimental.

Preparation of Thiazolidines.

2-Carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylic Acid.—A mixture of penicillamine hydrochloride (5 g.), methyl dimethoxyacetate (3·75 g.), and acetic acid (20 c.c.) was heated on the steam-bath for 30 minutes and then evaporated *in vacuo*, and the residue treated with aqueous potassium acetate and extracted with chloroform (4 × 25 c.c.). Evaporation of the extract gave a gum which crystallised on being rubbed with ether. *2-Carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylic acid* (5 g.) separated from ethyl acetate–light petroleum in laths, m. p. 140—142° (Found: C, 43·7; H, 6·2; N, 6·3. $C_8H_{13}O_4NS$ requires C, 43·8; H, 6·0; N, 6·4%).

The above thiazolidine (0·5 g.) was treated with an excess of ethereal diazomethane, and the product distilled in a high vacuum to yield an oil (0·45 g.) which was treated with ethereal hydrogen chloride. *Dimethyl 3 : 5 : 5-trimethylthiazolidine-2 : 4-dicarboxylate hydrochloride* crystallised from ethyl acetate–light petroleum in thin needles, m. p. 129—130° (Found: C, 41·7; H, 6·4. $C_{10}H_{18}O_4NClS$ requires C, 42·3; H, 6·4%). The base (0·95 g.) in methanol (10 c.c.) was hydrolysed with 0·1N-sodium hydroxide (40·7 c.c.), added in portions during 2—3 hours. The solution was washed with chloroform, just acidified with hydrochloric acid, and extracted with chloroform. Removal of the chloroform gave a gum which, in ether, with benzylamine afforded *benzylamine 4-carbomethoxy-3 : 5 : 5-trimethylthiazolidine-4-carboxylate* as laths, m. p. 164—165°, from methanol (Found: C, 56·6; H, 7·0; N, 7·9. $C_{16}H_{24}O_4N_2S$ requires C, 56·5; H, 7·1; N, 8·2%). This salt (0·5 g.) in water (10 c.c.) was treated with 0·5N-hydrochloric acid (3 c.c.), and the solution extracted with chloroform (4 × 10 c.c.). Evaporation of the extract gave *4-carbomethoxy-3 : 5 : 5-trimethylthiazolidine-4-carboxylic acid* (0·3 g.) which crystallised from ethyl acetate–light petroleum in laths, m. p. 145° (Found: C, 46·3; H, 6·5; N, 6·1. $C_9H_{15}O_4NS$ requires C, 46·3; H, 6·5; N, 6·0%).

4-Carbomethoxy-5 : 5-dimethylthiazolidine-2-carboxylic Acid.—(*a*) Penicillamine methyl ester hydrochloride (4 g.), potassium glyoxylate (3 g.), and acetic acid (40 c.c.) were heated together on the steam-bath for 40 minutes, and the solution was then evaporated *in vacuo*. Treatment of the residue in ethyl acetate with benzylamine gave benzylamine 4-carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylate (1·5 g.) which crystallised from ethyl acetate in needles, m. p. 143°, identical with the salt described below.

(*b*) Penicillamine methyl ester hydrochloride (150 g.), acetic acid (500 c.c.), and methyl dimethoxyacetate (100 g.) were heated together on the steam-bath for 3 hours, and then acetic acid was removed *in vacuo*. The residue was treated with excess of aqueous potassium hydrogen carbonate and extracted with chloroform (5 × 200 c.c.). Removal of the chloroform gave a pale brown oil (100 g.) which distilled at 110° in a high vacuum to yield *dimethyl 5 : 5-dimethylthiazolidine-2 : 4-dicarboxylate* as a viscous oil which solidified when set aside and crystallised from light petroleum in stout prisms, m. p. 70° (Found: C, 46·4; H, 6·8; N, 5·8. $C_9H_{15}O_4NS$ requires C, 46·3; H, 6·5; N, 6·0%). Mixing of ethereal solutions of hydrogen chloride and the thiazolidine gave the *hydrochloride* which separated from ethyl acetate–light

petroleum in needles, m. p. 138° (decomp.) (Found : C, 40·5; H, 6·0. $C_9H_{16}O_4NClS$ requires C, 40·1; N, 6·0%).

(i) The crude oily 2 : 4-dicarboxylate (1·14 g.) in methanol (15 c.c.) was hydrolysed with 0·1N-sodium hydroxide (48·4 c.c.), added in portions during 3 hours. The solution was acidified and extracted with chloroform, and the extract evaporated *in vacuo*. Treatment of the residue in ethyl acetate with benzylamine afforded *benzylamine* 4-*carbomethoxy*-5 : 5-*dimethylthiazolidine*-2-*carboxylate* (1 g.) which crystallised in needles, m. p. 143—144° (Found : C, 55·2; H, 6·8; N, 8·3. $C_{13}H_{22}O_4N_2$ requires C, 55·2; H, 6·8; N, 8·5%). (The D-form of this salt has been described by Merck, *M.* 66; *op. cit.*, p. 964). Addition of hydrochloric acid to the benzylamine salt (0·12 g.) in water, followed by extraction with chloroform and evaporation of the extract gave a gum which solidified when rubbed with ether. From ethyl acetate–light petroleum, 4-*carbomethoxy*-5 : 5-*dimethylthiazolidine*-2-*carboxylic acid* separated in fine needles, m. p. 115° (Found : C, 43·9; H, 6·1; N, 6·5; S, 14·6. $C_8H_{13}O_4NS$ requires C, 43·8; H, 6·0; N, 6·4; S, 14·6%).

(ii) The pure crystalline 2 : 4-dicarboxylate (26·5 g.) in methanol (100 c.c.) was hydrolysed with 0·5N-sodium hydroxide (215 c.c.), added in 10 portions during 3 hours. The solution was evaporated to low bulk *in vacuo* and then extracted with chloroform. The aqueous phase was acidified with 1·84N-hydrochloric acid (61 c.c.) and extracted with chloroform (6 × 60 c.c.). Evaporation of the chloroform layer gave a syrup, which after being seeded, set to a white solid (17 g.), m. p. 115°, identical with the 2-carboxylic acid described above.

Methyl 2-*Phenyl*-5 : 5-*dimethylthiazolidine*-4-*carboxylate*.—Penicillamine methyl ester hydrochloride (1·2 g.) and benzaldehyde (0·7 g.) were warmed together on the steam-bath. The initial syrup rapidly set to a white solid, m. p. 174° (decomp.), which was washed with ether. *Methyl* 2-*phenyl*-5 : 5-*dimethylthiazolidine*-4-*carboxylate hydrochloride* (1·4 g.) crystallised from chloroform–ether in prisms, m. p. 175° (decomp.) (Found : N, 4·9. $C_{13}H_{18}O_2NClS$ requires N, 4·9%). This ester did not dissolve in aqueous sodium hydrogen carbonate, unlike the corresponding thiazolidinecarboxylic acid hydrochloride of m. p. 172—173° (decomp.) (*op. cit.*, p. 962), and a mixture of the two had m. p. *ca.* 155° (decomp.). Copp, Duffin, Smith, and Wilkinson (*op. cit.*, p. 963; *CPS.* 688) give m. p. 154° for the methylthiazolidinecarboxylate hydrochloride.

Reactions with Acid Chlorides.

Reactions of 4-*Carbomethoxy*-5 : 5-*dimethylthiazolidine*-2-*carboxylic Acid*.—The thiazolidine (5 g.) in dry dioxan (40 c.c.) was treated with oxalyl chloride (5 g.) with cooling. After being kept overnight the solution was evaporated *in vacuo*, and the gum dissolved in ether. A white solid (3 g.) was gradually deposited. 4-*Carbomethoxy*-5 : 5-*dimethylthiazolidine*-2-*carboxylic*-3-*glyoxylic anhydride* (V) separated from ethyl acetate–light petroleum in needles, m. p. 128—130° (decomp.) (Found : C, 43·8; H, 4·2; N, 5·3. $C_{10}H_{11}O_6NS$ requires C, 43·9; H, 4·1; N, 5·1%). The anhydride (0·1 g.) was dissolved in warm water, and the solution evaporated *in vacuo* over phosphoric oxide to yield a solid residue. 4-*Carbomethoxy*-3-*oxalo*-5 : 5-*dimethylthiazolidine*-2-*carboxylic acid* (0·1 g.) crystallised from ethyl acetate–light petroleum in needles, m. p. 124—125° (decomp.) (Found : C, 40·9; H, 4·8; N, 4·9. $C_{10}H_{13}O_7NS$ requires C, 41·2; H, 4·5; N, 4·8%). 4-Carbomethoxy-5 : 5-dimethylthiazolidine-2-carboxylic acid (3 g.) in dry pyridine (15 c.c.) was treated with oxalyl chloride (2·5 g.) with cooling. A vigorous reaction occurred with formation of a dark brown solution and precipitate, and carbon dioxide was evolved. After being kept overnight at room temperature the solution was heated on the steam-bath for 10 minutes and then evaporated *in vacuo*. The dark brown residue was dissolved in chloroform (150 c.c.), and the solution washed with 2% aqueous sodium hydrogen carbonate (25 c.c.), 0·5N-hydrochloric acid (2 × 25 c.c.), and water (2 × 25 c.c.). The dried chloroform solution was evaporated to small bulk (10 c.c.), and the solution passed through a column of alumina. A brown band passed rapidly down the column, much dark material being adsorbed at the top. Evaporation of the eluate afforded a brown gum which became powdery when rubbed with ether. The *compound* (0·3 g.) crystallised from chloroform–light petroleum in plates, m. p. 225—230° (decomp.) (Found : C, 49·7, 48·15; H, 5·4, 5·3; N, 6·35; S, 14·4. $C_9H_{11}O_4NS$ requires C, 47·2; H, 4·8; N, 6·15; S, 14·0. $C_{16}H_{22}O_6N_2S_2$ requires C, 47·8; H, 5·5; N, 7·0; S, 15·9%). 4-Carbomethoxy-5 : 5-dimethylthiazolidine-2-carboxylic acid (3·0 g.) in pyridine (15 c.c.) was treated with oxalyl chloride (2·5 g.) with cooling. After working up as described above, *dimethyl* 3 : 6-*diketo*-5′ : 5′ : 5″ : 5″-*tetramethyldithiazolidino*(3′ : 2′-1 : 2)(3″ : 2″-4 : 5)*piperazine*-4′ : 4″-*dicarboxylate* (VII) crystallised from chloroform–light petroleum in laths, m. p. 170° (Found : C, 47·8; H, 5·5; N, 7·1; S, 15·8. $C_{16}H_{22}O_6N_2S_2$ requires C, 47·8; H, 5·5; N, 7·0; S, 15·9%). 4-Carbomethoxy-5 : 5-dimethylthiazolidine-2-carboxylic acid (0·3 g.) in pyridine (5 c.c.) was treated with toluene-*p*-sulphonyl chloride (0·4 g.), and the solution heated on the steam-bath for 30 minutes. The solution was evaporated to dryness *in vacuo*, and the residue dissolved in chloroform and washed with N-hydrochloric acid and 5% aqueous sodium hydrogen carbonate. Evaporation of the dried chloroform solution *in vacuo* gave a syrup which crystallised when rubbed with ethanol. The isomeric *diketopiperazine* (0·1 g.) separated from ethanol in needles, m. p. 195—197° (Found : C, 48·3; H, 5·5. $C_{16}H_{22}O_6N_2S_2$ requires C, 47·8; H, 5·5%). The same compound was obtained by use of benzenesulphonyl chloride.

Reactions with 2-*Carbomethoxy*-5 : 5-*dimethylthiazolidine*-4-*carboxylic Acid*.—This compound (1·0 g.) in chloroform (5 c.c.) containing pyridine (1·5 c.c.) was kept for 2 hours with ethoxalyl chloride (0·7 g.). The solution was evaporated, excess of aqueous sodium hydrogen carbonate added, and the solution extracted with ether. The aqueous phase was acidified and again extracted with ether, the extract giving a gum which solidified to white needles. 2-*Carbomethoxy*-3-*ethoxalyl*-5 : 5-*dimethylthiazolidine*-4-*carboxylic acid hydrate* separated from ethyl acetate–light petroleum and then had m. p. 95° (yield, 0·5 g.) (Found : C, 43·3; H, 6·0; N, 4·3. $C_{12}H_{17}O_7NS,H_2O$ requires C, 42·8; H, 5·7; N, 4·15%). This acid (0·1 g.) was treated with excess of ethereal diazomethane, and the solution evaporated to give *dimethyl* 3-*ethoxalyl*-5 : 5-*dimethylthiazolidine*-2 : 4-*dicarboxylate* (0·1 g.) which separated from light petroleum in hexagonal prisms, m. p. 93—94° (Found : C, 46·7; H, 5·8; N, 4·1. $C_{13}H_{19}O_7NS$ requires C, 46·8; H, 5·7; N, 4·2%). 2-Carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylic acid (1·0 g.) in dry dioxan (2 c.c.) was treated with oxalyl chloride (0·8 c.c.) with cooling. A white solid (0·7 g.) was gradually deposited.

2-Carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylic-3-glyoxylic anhydride (IX; R = CO_2Me, R′ = H) separated from ethyl acetate–light petroleum in needles, m. p. 173—175° (decomp.) (Found : C, 43·7; H, 4·25; N, 5·3. $C_{10}H_{11}O_6NS$ requires C, 43·9; H, 4·1; N, 5·1%). The anhydride (0·1 g.) was dissolved in dry ethanol (1 c.c.), and the solution evaporated *in vacuo*. The resultant gum crystallised completely (yield, 0·12 g.). After recrystallisation from ethyl acetate–light petroleum it had m. p. 94—95°, undepressed by the 3-ethoxalyl-4-carboxylic acid described above. The anhydride (0·1 g.) was dissolved in warm water (0·3 c.c.), and the clear solution evaporated *in vacuo* over phosphoric oxide. A portion of the residual gum was dissolved in dry ether (the anhydride was insoluble in this solvent), and the solution treated with benzylamine (0·1 g.), whereupon the *bisbenzylamine 2-carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylate-3-glyoxylate* (0·1 g.) was obtained in white laths, m. p. 204—205° (decomp.), from methanol–ether (Found : C, 57·3; H, 6·5; N, 7·9. $C_{24}H_{31}O_7N_3S$ requires C, 57·0; H, 6·2; N, 8·3%). The remainder of the gum crystallised from dry ether–pentane to give prisms, m. p. 157° (decomp.), of *2-carbomethoxy-3-oxalo-5 : 5-dimethylthiazolidine-4-carboxylic acid* (Found : C, 41·7; H, 4·8. $C_{10}H_{13}O_7NS$ requires C, 41·2; H, 4·5%). 2-Carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylic acid (2·0 g.) was dissolved in pure dry pyridine (15 c.c.) cooled to 0°, and added slowly with stirring to the ice-cold complex from oxalyl chloride (1·4 g.) and dry pyridine (15 c.c.). The mixture became coloured, and the addition complex dissolved with effervescence. After being kept overnight at 0° (some solid separated), the mixture was warmed for 30 minutes on the steam-bath and evaporated to dryness *in vacuo*. The brown residue was dissolved in chloroform and extracted with N-hydrochloric acid (2 × 15 c.c.) and saturated sodium hydrogen carbonate solution (2 × 15 c.c.); after being washed with water, the chloroform layer was dried, evaporated to 20 c.c., and passed through alumina, a brownish-coloured eluate being collected in two portions. These were separately evaporated, and treated with dry ether to yield, respectively, 95 mg. of pale buff-coloured solid (m. p. 175—180°) and 120 mg. (m. p. 170—180°). These solids, insoluble in aqueous ammonium hydrogen carbonate, were combined and dissolved in chloroform, and the solution was treated with light petroleum. After an initial flocculent precipitate had been rejected, and on cooling and scratching, the liquor deposited needles, m. p. 195—197°. Following several recrystallisations, the *product* had m. p. 202—203° (Found, on different preparations : C, 47·0, 47·6; H, 4·4, 4·4; N, 6·15; S, 14·2. $C_9H_{11}O_4NS$ requires C, 47·2; H, 4·8; N, 6·15; S, 14·0%). Light absorption (chloroform) : Max., 2640 A.; $E^{1\%}_{1\,cm.}$ = 460. 2-Carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylic acid (2·0 g.) in pyridine (10 c.c.) was warmed with toluene-*p*-sulphonyl chloride (2·0 g.) for 20 minutes and kept overnight at room temperature. After evaporation to dryness *in vacuo*, the residue was dissolved in chloroform and washed with 2N-hydrochloric acid, sodium hydrogen carbonate, and water, and the chloroform extract re-evaporated. The crystalline residue, m. p. 175—180°, was washed with ether and recrystallised, first from ethanol and then from chloroform–light petroleum, to yield *dimethyl 3 : 6-diketo-5′ : 5′ : 5″ : 5″-tetramethyldithiazolidino(3′ : 4′-1 : 2)(3″ : 4″-4 : 5)piperazine-2′ : 2″-dicarboxylate* (X; R = H, R′ = CO_2Me) as white laths, m. p. 186—187° (to an opaque liquid which cleared at 204—205°) (Found : C, 46·9; H, 4·8; N, 6·95. $C_{16}H_{22}O_6N_2S_2$ requires C, 47·8; H, 5·5; N, 7·0%). The preparation was repeated using benzenesulphonyl chloride (1·6 g.). The diketopiperazine crystallised from chloroform–light petroleum in short prisms, m. p. 186—187° (clearing at 190°) not depressed on admixture with the previous specimen (Found : C, 47·9; H, 5·5; N, 6·5%).

Reactions of 2 : 5 : 5-Trimethyl-2-carbethoxymethylthiazolidine-4-carboxylic Acid.—The thiazolidine (0·3 g.) (Clayton, Elks, Hems, and Robinson, *CPS.* 201; *op. cit.*, p. 965), dissolved in dried pyridine (15 c.c.), was cooled in ice and added slowly to an ice-cold mixture of oxalyl chloride (3·3 c.c.) and dry pyridine (7 c.c.). A vigorous reaction took place as addition proceeded, with much charring. A solid black mass formed which, on being broken up, appeared to redissolve with effervescence. After being kept overnight at room temperature the mixture was evaporated to dryness and treated with chloroform containing ethanol. The solution was extracted with dilute hydrochloric acid and then with aqueous sodium hydrogen carbonate, and washed with water. Acidification of the sodium hydrogen carbonate extract, after treatment with charcoal, gave an oil which crystallised after a few days. On dissolution in ether and dilution with pentane, *3-ethoxalyl-2 : 5 : 5-trimethyl-2-carbethoxymethylthiazolidine-4-carboxylic acid* formed colourless laths which after further crystallisation had m. p. 137—138° (Found : C, 50·0; H, 6·5; N, 4·1; S, 9·4. $C_{15}H_{23}O_7NS$ requires C, 49·9; H, 6·4; N, 3·9; S, 8·9%). After chromatography of the neutral fraction from the chloroform–ethanol, a white solid (600 mg.), m. p. 175°, was obtained. The compound crystallised from ethyl acetate in massive prisms or cubes, m. p. 199—200°, and showed no depression in m. p. when mixed with the *3 : 6-diketo-2′ : 5′ : 5′ : 2″ : 5″ : 5″-hexamethyl-2′ : 2″-di(carbomethoxymethyl)dithiazolidino(3′ : 4′-1 : 2)(3″ : 4″-4 : 5)piperazine* prepared in good yield from the thiazolidine and toluene-*p*-sulphonyl chloride in the usual way (Found : C, 54·6; H, 6·8; N, 5·75; S, 13·6. $C_{22}H_{34}O_6N_2S_2$ requires C, 54·3; H, 7·0; N, 5·75; S, 13·2%).

Reactions with 2-Phenyl-5 : 5-dimethylthiazolidine-4-carboxylic Acid.—The thiazolidine (Clayton, Elks, Hems, and Robinson, *CPS.* 201; *op. cit.*, p. 962) was dissolved in dry dioxan (25 c.c.), and oxalyl chloride (1·8 g.) added with cooling. After 1 hour, the solution was evaporated *in vacuo*, and the gum treated with ether, whereupon rapid crystallisation occurred. *2-Phenyl-5 : 5-dimethylthiazolidine-4-carboxylic-3-glyoxylic anhydride* separated from ethyl acetate–light petroleum in hexagonal plates, m. p. 145° (decomp.) (yield, 1·7 g.) (Found : C, 57·7; H, 4·5; N, 5·1. $C_{14}H_{13}O_4NS$ requires C, 57·7; H, 4·5; N, 4·8%). The anhydride (0·5 g.) was heated with ethanol for 1—2 minutes. The clear solution was evaporated *in vacuo*, and the gum crystallised from ether–light petroleum. Two kinds of crystals were deposited, which were separated mechanically. *4-Carbethoxy-2-phenyl-5 : 5-dimethylthiazolidine-3-glyoxylic acid* formed rosettes, m. p. 157—158° (decomp.) (yield, 0·2 g.) (Found : C, 56·0; H, 5·7; N, 4·5. $C_{16}H_{19}O_5NS$ requires C, 56·9; H, 5·7; N, 4·1%), and *3-ethoxalyl-2-phenyl-5 : 5-dimethylthiazolidine-4-carboxylic acid*, needles, m. p. 140° (decomp.) (yield, 0·3 g.) (Found : C, 56·4; H, 6·0. $C_{16}H_{19}O_6NS$ requires C, 56·9; H, 5·7%). 2-Phenyl-5 : 5-dimethylthiazolidine-4-carboxylic acid (1·0 g.) was dissolved in chloroform (5 c.c.) containing pyridine (1·5 c.c.) and treated with ethoxalyl chloride (1·0 g.) with cooling. After 2 hours, the solution was evaporated to small bulk *in vacuo*, excess of aqueous sodium hydrogen carbonate was added, and the solution extracted with ether. The aqueous phase was acidified with hydrochloric acid and again extracted with ether. Evaporation of the ether yielded the 3-ethoxalyl

derivative as a white crystalline powder (0·9 g.) which crystallised from ether–light petroleum in needles, m. p. 140° (decomp.), undepressed on admixture with the needles described above. 2-Phenyl-5 : 5-dimethylthiazolidine-4-carboxylic acid (7·5 g.) in dry pyridine (40 c.c.) was treated with oxalyl chloride (3·7 c.c.) in pyridine (10 c.c.). The reaction mixture was worked up in the normal way, and after chromatography, a white solid (250 mg.), m. p. 220—225°, was obtained. On recrystallisation from chloroform–light petroleum, 3 : 6-*diketo*-2′ : 2″-*diphenyl*-5′ : 5′ : 5″ : 5″-*tetramethyldithiazolidino*(3′ : 4′-1 : 2)(3″ : 4″-4 : 5)*piperazine* (X; R = H, R′ = Ph) was obtained in clusters of laths, m. p. 240—241° (Found : C, 65·2; H, 5·9; N, 5·95; S, 14·25. $C_{24}H_{24}O_2N_2S_2$ requires C, 65·8; H, 5·9; N, 6·4; S, 14·6%). This compound (70 mg.) was heated under reflux with glacial acetic acid (3 c.c.) and concentrated hydrochloric acid (2 c.c.) overnight; on cooling, a crystalline solid (50 mg.), m. p. 255—258°, separated. This, an isomeric *diketopiperazine*, crystallised from chloroform–light petroleum in long needles, m. p. 263—264° (Found : C, 65·3; H, 6·0; N, 5·8%), depressed to 240—250° on admixture with the previous diketopiperazine. 2-Phenyl-5 : 5-dimethylthiazolidine-4-carboxylic acid (1·3 g.) in pyridine (10 c.c.) was treated with toluene-*p*-sulphonyl chloride (1·0 g.). The solution was warmed for 10 minutes; a pink colour developed and white crystals slowly separated (300 mg., m. p. 268—271°). Recrystallisation from chloroform–light petroleum gave a diketopiperazine as fine needles, m. p. 270—271° (Found : C, 65·5; H, 6·3; N, 6·5. Calc. for $C_{24}H_{24}O_2N_2S_2$: C, 65·8; H, 5·9; N, 6·4%), which showed no depression in m. p. when mixed with the previously described compound of m. p. 263—264°. Acidification of the sodium hydrogen carbonate extract from preparation of the diketopiperazine of m. p. 240—241° gave a solid acid which was partly purified by dissolution in sodium hydrogen carbonate (charcoal), re-acidification, and dissolution in ether, some brown insoluble material being removed. The clear yellow solution was treated with a slight excess of ethereal diazomethane and evaporated to small bulk, and the solid, m. p. 192—196°, was collected. *Oxalylbis*-3-(4-*carbomethoxy*-2-*phenyl*-5 : 5-*dimethylthiazolidine*) crystallised from dioxan–water in cubes, m. p. 205—206° (Found : C, 60·0; H, 5·8; N, 4·7. $C_{28}H_{32}O_6N_2S_2$ requires C, 60·4; H, 5·8; N, 5·0%).

Reactions of Methyl 2-*Phenyl*-5 : 5-*dimethylthiazolidine*-4-*carboxylate*. The thiazolidine hydrochloride (2·9 g.) in chloroform was shaken with aqueous potassium acetate, and the oily base, obtained by evaporating the dried chloroform solution, was treated with oxalyl chloride (1·3 g.) in dry dioxan (20 c.c.). After 30 minutes, the solution was evaporated *in vacuo*, and the residue stirred with ether and light petroleum. Recrystallisation from chloroform–light petroleum afforded prisms (0·7 g.), m. p. 208°, of an isomeric *oxalylbis*-3-(4-*carbomethoxy*-2-*phenyl*-5 : 5-*dimethylthiazolidine*) (Found : C, 60·0; H, 5·6; N, 5·0%; *M*, cryoscopic in camphor, 544). Mixed with the preceding isomer, the m. p. was depressed to 185—204°. The mother-liquors were washed with aqueous sodium hydrogen carbonate and the gummy neutral material chromatographed in ether on alumina to yield a third *oxalylbis*-3-(4-*carbomethoxy*-2-*phenyl*-5 : 5-*dimethylthiazolidine*) (0·5 g.), crystallising from acetone–light petroleum in needles, m. p. 167—168° (Found : C, 60·4; H, 5·9; N, 4·7%; *M*, cryoscopic in camphor, 567).

Reactions of 2 : 2 : 5 : 5-*Tetramethylthiazolidine*-4-*carboxylic Acid*.—The thiazolidine hydrochloride (10 g.) (McOmie, Abraham, Baker, Chain, and Robinson, *CPS*. 32; these authors give a better description than that previously recorded, *op. cit.*, pp. 463—464) was stirred with oxalyl chloride (12 g.) and dry dioxan (150 c.c.) for 48 hours. Unchanged material (mixed m. p.) was collected (3·6 g.) and the filtrate evaporated *in vacuo* to yield a crystalline solid (3·6 g.) which was washed free from oil with dry ether. From dry dioxan—ether, 2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic*-3-*glyoxylic anhydride* formed prisms, m. p. 160° (decomp.) (Found : C, 49·6; H, 5·5. $C_{10}H_{13}O_4NS$ requires C, 49·4; H, 5·35%). The anhydride (0·5 g.) was warmed with ethanol (5 c.c.) and the solution evaporated *in vacuo*. The gum was dissolved in ether, and light petroleum was added, whereupon crystals separated. 3-*Ethoxalyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic acid* (0·4 g.) separated from ether–light petroleum in lath clusters, m. p. 119—120° (decomp.) (Found : C, 49·8; H, 6·6; N, 4·8; S, 11·35. $C_{12}H_{19}O_5NS$ requires C, 49·8; H, 6·6; N, 4·8; S, 11·1%). 2 : 2 : 5 : 5-Tetramethylthiazolidine-4-carboxylic acid (1 g.) in chloroform (5 c.c.) containing pyridine (1·5 c.c.) was treated with ethoxalyl chloride (1 g.) with cooling. After 3 hours the solution was evaporated *in vacuo*, and the gum treated with aqueous sodium hydrogen carbonate and extracted with ether. The aqueous phase was acidified and extracted with ether. Evaporation of the latter extract gave the 3-ethoxalyl derivative as a white solid (0·8 g.) which after recrystallisation from ether–light petroleum had m. p. 120—121°, undepressed in admixture with the previously described ethoxalyl compound. By heating the authentic 3-ethoxalyl derivative with an excess of benzylamine in dioxan for 30 minutes on the steam-bath, cooling the mixture, and adding dilute aqueous hydrochloric acid, the 3-oxalylbenzylamide was obtained, crystallising from aqueous ethanol in square plates, m. p. 104—105°, identical with the benzylamide next prepared. Reaction of the anhydride with benzylamine in the absence of solvent gave, after treatment with dilute aqueous hydrochloric acid, 3-N-*benzyloxamyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic acid* (XV) which crystallised from aqueous ethanol in hydrated square plates, m. p. 105—106° (Found : C, 55·3; H, 6·6; N, 7·5. $C_{17}H_{22}O_4NS,H_2O$ requires C, 55·4; H, 6·5; N, 7·6%). When the anhydride was first dissolved in dioxan and then treated with benzylamine, 3-*oxalo*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxybenzylamide* was obtained on acidification; it crystallised from dioxan–water in long laths, m. p. 134—135° (Found : C, 58·0; H, 6·8; N, 7·2. $C_{17}H_{22}O_4NS$ requires C, 58·3; H, 6·3; N, 8·0%). With methanol, the anhydride reacted to form 3-*methoxalyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic acid* which separated from ether–pentane in prisms, m. p. 136—137° (Found : C, 47·6; H, 6·3; N, 5·0. $C_{11}H_{17}O_5NS$ requires C, 48·0; H, 6·2; N, 5·1%). Esterification with diazomethane gave the dimethyl ester, m. p. 83°, described below. The anhydride dissolved slowly in cold water to afford 3-*oxalo*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic acid* which crystallised from a little ether, on addition of pentane, in prisms, m. p. 139° (decomp.) (Found : C, 45·7; H, 5·9; N, 5·1. $C_{10}H_{15}O_5NS$ requires C, 46·0; H, 5·75; N, 5·4%). By treating this di-acid with diazomethane in ether, *methyl* 3-*methoxalyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylate* was obtained, which crystallised from methanol–water in long needles, m. p. 83° (Found : C, 49·35; H, 6·6; N, 4·6. $C_{11}H_{19}O_5NS$ requires C, 49·8; H, 6·6; N, 4·8%). 2 : 2 : 5 : 5-Tetramethylthiazolidine-4-carboxylic acid hydrochloride (11·0 g.) was dissolved in dry pyridine (75 c.c.), the solution cooled to 0° and added slowly, with stirring, to a mixture of oxalyl

chloride (6·5 c.c.) and ice-cold pyridine (25 c.c.). A vigorous reaction took place, a hard black mass forming, which redissolved with effervescence. The mixture was set aside overnight at 0° and then evaporated to dryness *in vacuo*, and the black residue dissolved in chloroform (100 c.c.). The solution was extracted with 2N-hydrochloric acid (2 × 50 c.c.) and saturated aqueous sodium hydrogen carbonate (2 × 50 c.c.). The chloroform layer was dried and evaporated, and the residue, redissolved in dry chloroform (35 c.c.), was passed through a column of alumina. Evaporation of the brownish eluate gave a partly crystalline residue which was washed with ethanol–ether (1 : 1) to yield a white solid (800 mg.), m. p. 245—255°. On recrystallisation from hot ethanol, 3 : 6-*diketo*-2′ : 2′ : 5′ : 5′ : 2″ : 2″ : 5″ : 5″-*octamethyldithiazolidino*(3′ : 4′-1 : 2)(3″ : 4″-4 : 5)*piperazine* formed square plates, m. p. 262—263° (Found : C, 56·05; H, 7·7; N, 7·65. $C_{16}H_{24}O_2N_2S_2$ requires C, 56·1; H, 7·6; N, 7·6%).

Reactions of Methyl 2 : 2 : 5 : 5-*Tetramethylthiazolidine*-4-*carboxylate*.—The compound (6 g.) (Copp, Duffin, Smith, and Wilkinson, *CPS*. 19; *op. cit.*, p. 960) was treated with oxalyl chloride (8 g.) in dry dioxan (60 c.c.). After 2·5 hours the solution was evaporated *in vacuo*, and the dark residue triturated with ether. From acetone (charcoal) on addition of water, *oxalylbis*-3-(4-*carbomethoxy*-2 : 2 : 5 : 5-*tetramethylthiazolidine*) (0·8 g.) separated in fine laths, m. p. 173—174° (Found : C, 52·2; H, 7·2; N, 5·9%; *M*, cryoscopic in camphor, 388. $C_{20}H_{32}O_6N_2S_2$ requires C, 52·2; H, 7·0; N, 6·1%; *M*, 460). By extracting the filtrates with aqueous sodium hydrogen carbonate, acidifying the extract, back-extracting with ether, and evaporating the ethereal solution *in vacuo*, *methyl* 3-*oxalo*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylate* (1·5 g.) was obtained and crystallised from ether–pentane (charcoal) in prisms, m. p. 112° (decomp.) (Found : C, 48·0; H, 6·45; N, 5·1. $C_{11}H_{17}O_5NS$ requires C, 48·0; H, 6·2; N, 5·1%). Treatment of this acid with ethereal diazomethane gave methyl 3-methoxalyl-2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylate, m. p. 83°, identical with the preparation already described.

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499. *Syntheses in the Penicillin Field. Part II. The Anhydrides of 4-Carbomethoxy-3-oxalo-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic Acid.*

By R. BENTLEY, A. H. COOK, and J. A. ELVIDGE.

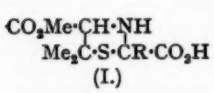
Penicillamine methyl ester was condensed with α-keto*iso*butyric acid to afford two stereoisomeric 4-*carbomethoxy*-5 : 5-*dimethyl*-2-iso*propylthiazolidine*-2-*carboxylic acids* (I; R = Pr^i). With oxalyl chloride in dioxan, these gave two *thiazolidine*-2-*carboxylic*-3-*glyoxylic anhydrides*, each of which formed its own series of *products* on ring scission, *e.g.*, with water and ethanol. The action of heat on certain products was examined and also the possibility of effecting ring-contraction of the anhydrides by thermal elimination of carbon dioxide.

THIAZOLIDINE-2-CARBOXYLIC ACIDS react smoothly in dioxan with oxalyl chloride to yield, as major products, thiazolidine-2-carboxylic-3-glyoxylic anhydrides, *e.g.*, (I; R = H) ⟶ (II; R = H) (preceding paper). Thiazolidine keto-β-lactams (III; R = H), required as intermediates for a synthesis of penicillins, did not appear to be forthcoming directly from these reactions, and the possibility was therefore examined of eliminating the elements of carbon dioxide from the available anhydrides in order to effect ring-contraction to the desired lactams.

Of α-keto-acids, required for condensation with penicillamine to form thiazolidine-2-carboxylic acids, α-keto*iso*butyric acid was the most easily accessible, being readily obtained from 2-phenyl-4-*iso*propylideneoxazolone, an intermediate in the manufacture of penicillamine. Consequently, the feasibility of the proposed ring-contraction was examined largely with the aid of the 3-glyoxylic anhydrides (see below) prepared from the two forms (*A*, *B*), doubtless stereoisomerides, of 4-*carbomethoxy*-5 : 5-*dimethyl*-2-iso*propylthiazolidine*-2-*carboxylic acid* (I; R = Pr^i) which arose from the condensation of α-keto*iso*butyric acid and penicillamine methyl ester.

The higher-melting form (*A*) reacted with oxalyl chloride in dioxan to give the *anhydride* (II; R = Pr^i) (*form* A) which led, as in previous analogous cases of ring scission (preceding paper), to the *oxalo-acid* (IV; R = R′ = H) (*form* A) and the *ethoxalyl* compound (IV; R = Et, R′ = H) (*form* A). The lower-melting form (I; R = Pr^i) similarly afforded an *anhydride* (II; R = Pr^i) (*form* B) and thence with water and ethanol the *products* (IV; R = R′ = H) and (IV; R = Et, R′ = H) (*forms* B). The ethoxalyl derivatives (IV; R = Et, R′ = H)

(forms *A* and *B*) were also prepared from the parent thiazolidines (I; R = Pr^{i}) (forms *A* and *B*) and ethoxalyl chloride. Since, however, form *A* of (IV; R = Et, R′ = H) melted with decomposition, a derivative more suitable for purposes of comparison was required. The ethoxalyl compounds *A* from the two sources (I; R = Pr^{i}) and (II; R = Pr^{i}) were therefore treated with diazomethane, whereupon each afforded the same *ester* (IV; R = Et, R′ = Me) (*form* A). Similar esterification of (IV; R = R′ = H) (form *A*) gave the *derivative* (IV; R = R′ = Me) which was also obtained by treating the anhydride (II; R = Pr^{i}) (form *A*)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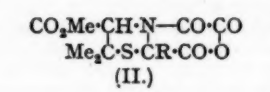
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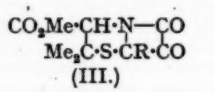
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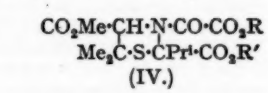
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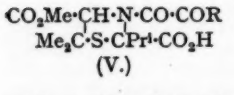
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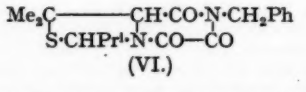
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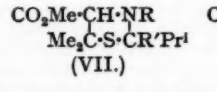
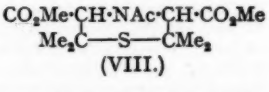

(VII.)


(VIII.)

with methanol to yield an *acid*, presumably (IV; R = Me, R′ = H) and then esterifying this with diazomethane. Form *A* of the anhydride (II; R = Pr^{i}) with 2 : 4-dinitrophenylhydrazine in dry dioxan afforded a *hydrazide-acid* and with benzylamine a *benzylamide-acid*, very probably [V; R = NH·NH·C$_6$H$_3$(NO$_2$)$_2$ and NH·CH$_2$Ph, respectively]. In addition, a neutral *substance* was isolated from the latter reaction, the same material being obtained also from form *B* of the anhydride (II; R = Pr^{i}) and benzylamine in the absence of a solvent; on the basis of properties and analyses, structure (VI) is proposed. The formation of a neutral benzylamine derivative, rather than acidic products, from the anhydrides may be attributed to a secondary change occasioned by the vigour of reaction when using undiluted reactants, *viz.*, (V; R = NH·CH$_2$Ph) ⟶ (VI) + MeOH + CO$_2$. Production of only one compound from both forms of the anhydrides suggests that decarboxylation at the 2-position of the thiazolidine ring can result in spatial readjustment. Support for this view was provided by the behaviour of the stereoisomeric thiazolidines (I; R = Pr^{i}) (forms *A* and *B*) when they were boiled under reflux in ψ-cumene : both isomers were decarboxylated, giving rise to the same product, isolated as a crystalline *hydrochloride* of m. p. 180°. Incidentally, this compound was at first thought to differ from the expected hydrochloride of (VII; R = H, R′ = H) since interaction of penicillamine methyl ester with *iso*butyraldehyde afforded a *hydrochloride* of m. p. 167°. However, a mixture of the two hydrochlorides had unchanged melting point, and the former salt underwent scission with mercuric chloride to yield penicillamine methyl ester and *iso*-butyraldehyde (identified as the 2 : 4-dinitrophenylhydrazone). Furthermore, after the oily base from the lower-melting salt had been heated under reflux in ψ-cumene, the higher-melting hydrochloride was obtained. Hence it is concluded that the latter represents a pure stereoisomer and that, if configurational changes are possible, as in the above cases, the more stable stereoisomer is obtained at elevated temperatures. The pure *stereoisomer* (VII; R = Ac, R′ = CO$_2$Me), prepared from (I; R = Pr^{i}) (form *A*) by acetylation to the *derivative* (VII; R = Ac, R′ = CO$_2$H) and subsequent methylation, was unchanged by boiling ψ-cumene. That ring expansion might occur to yield the symmetrical thiomorpholine (VIII) was considered a possibility but was not realised. Heating form *A* of the oxalo-acid (IV; R = R′ = H) in xylene caused loss of carbon monoxide and dioxide, and (I; R = Pr^{i}) (form *A*) was the sole product. There is therefore an appreciable difference in thermal stability between the carboxyl group of the 3-oxalo-substituent and that in the 2-position of the thiazolidine ring, since the latter was eliminated only at the boiling point of ψ-cumene. Compound (IV; R = R′ = H) (form *A*) also lost carbon monoxide and dioxide, when treated with mercuric chloride at ordinary temperature, the thiazolidine ring simultaneously undergoing hydrolytic scission to yield α-keto*iso*butyric acid and penicillamine methyl ester.

In preliminary attempts to effect elimination of carbon dioxide from the anhydride (II; R = Pr^{i}) (form *A*) by boiling it in xylene or pyridine, and by heating it with powdered glass at 100—160° in the absence of a solvent, the thiazolidine (I; R = Pr^{i}) (form *A*) was obtained, presumably because traces of water had been present, giving rise to the oxalo-acid (IV; R = R′ = H) as an intermediate. Also obtained by heating (II; R = Pr^{i}) (form *A*) with powdered glass were a distillable oil, possibly (VII; R = CHO, R′ = H)—the authentic *compound* prepared from the hydrochloride of (VII; R = H, R′ = H) was an oil—and gummy products. The carbon dioxide evolved amounted to 0·38—0·54 mol. From the gummy material, crystalline unchanged anhydride (II; R = Pr^{i}) (form *A*) was isolated directly, or the acid (IV; R = Et, R′ = H) (form *A*) after treating the original mixture with ethanol, whilst

reaction with methanolic or aqueous mercuric chloride, followed by addition of 2 : 4-dinitrophenylhydrazine, afforded the 2 : 4-*dinitrophenylhydrazones* of α-keto*iso*butyric acid and its methyl ester.

Re-investigation of the thermal behaviour of the anhydrides (II; R = Pr^i) emphasised their reactivity towards water, and particular care was necessary to prevent access of moisture and consequent formation of the ring-scission products (IV; R = R′ = H) which decompose thermally with gas evolution. Thus under strictly anhydrous conditions, no decomposition occurred when the anhydrides (II; R = Pr^i) (forms *A* and *B*) were boiled under reflux in xylene or ψ-cumene. Nor did the recrystallised anhydrides decompose at their melting points, a notable difference from the crude solids (as initially isolated from the oxalyl chloride reaction). However, when the anhydride *A* was heated with dried thoria, both carbon dioxide and carbon monoxide were evolved, but curiously enough the oxalo-acid (IV; R = R′ = H) (form *A*) was isolated (as its *bisbenzylamine* salt) from the reaction mixture. With copper-bronze as catalyst, only carbon dioxide was evolved (as desired), but unfortunately the product appeared to be polymeric; when dry xylene was employed as a diluent, no gas evolution took place. When (II; R = Pr^i) (form *A*) was heated at 140° with dried powdered glass and the light petroleum-soluble portion of the product fractionally distilled in a high vacuum, the crystalline acid (VII; R = CHO, R′ = CO_2H) was isolated and identified with an authentic specimen prepared from (I; R = Pr^i) (form *A*). An oil, also obtained from the distillation, gave a 2 : 4-dinitrophenylhydrazone which became resinous and could not be purified.

In view of the thermal behaviour of the 3-oxalo-acid (IV; R = R′ = H) (form A) which loses both carbon monoxide and dioxide, it is uncertain how the *N*-formyl compounds (VII; R = CHO, R′ = H and CO_2H) arose. It is conceivable, however, that they were formed from the required keto-β-lactam (III; R = Pr^i) by hydrolytic scission during isolation, followed by decarboxylation in the case of (VII; R = CHO, R′ = H). It is also possible that (III; R = Pr^i) was present in the oil which was isolated and gave rise to the unstable 2 : 4-dinitrophenylhydrazone. In view of the repeated failures to obtain more tangible evidence for the formation of a keto-β-lactam, it became clear that the desired ring contraction was not being effected to any degree potentially useful and the investigation was therefore discontinued.

Experimental.

*4-Carbomethoxy-5 : 5-dimethyl-2-iso*propylthiazolidine-2-carboxylic Acids.*—Penicillamine methyl ester hydrochloride (10 g.) and α-keto*iso*butyric acid (7·0 g.) (Ramage and Simonsen, *J.*, 1935, 534) were warmed in a little methanol for 10 minutes on the steam-bath. The viscous gum was washed with dry ether; the ethereal washings very slowly deposited crystals of *4-carbomethoxy-5 : 5-dimethyl-2-iso*propylthiazolidine-2-carboxylic acid hydrochloride* which crystallised from ethyl acetate in compact clumps of prisms, m. p. 129—130° (decomp.) (Found: N, 4·6. $C_{11}H_{20}O_4NClS$ requires N, 4·7%). To the gum, water (100 c.c.) was added slowly with stirring. After several hours, the resulting solid (7·5 g.), m. p. 155—160° (decomp.), was collected and recrystallised from aqueous ethanol to yield *4-carbomethoxy-5 : 5-dimethyl-2-iso*propylthiazolidine-2-carboxylic acid (form* A) as plates (parallelograms), m. p. 180—181° (decomp.) (Found: C, 50·3; H, 7·5; N, 5·6. $C_{11}H_{19}O_4NS$ requires C, 50·6; H, 7·3; N, 5·4%). An excess of potassium acetate was added to the filtrate, and the solution extracted with chloroform. Evaporation of the latter *in vacuo* gave a crystalline residue (1·9 g.), m. p. 125—130°, which was washed with pentane–ether. The isomeric *thiazolidine-acid (form* B) crystallised from benzene in fine needles, m. p. 123—125° (decomp.) (Found: C, 50·9; H, 7·3; N, 5·25%). Penicillamine methyl ester hydrochloride (2·0 g.), α-keto*iso*butyric acid (1·2 g.), and potassium acetate (1·0 g.) were dissolved in water (25 c.c.); the clear solution quickly became cloudy, depositing an oil which crystallised when cooled and scratched. The solid (1·7 g.), m. p. 125—127°, was recrystallised from benzene to form fine needles, m. p. 125—127° (decomp.), undepressed when mixed with form *B* above.

Anhydrides.—The thiazolidine (form *A*) (1·5 g.) was dissolved in dry dioxan (10 c.c.), and oxalyl chloride (1·2 c.c.) was added dropwise with cooling. The clear solution was kept overnight at room temperature and evaporated to dryness *in vacuo*, and the crystalline residue recrystallised several times from dry xylene and dry chloroform–pentane, to yield prismatic needles, m. p. 137—138°, of *4-carbomethoxy-5 : 5-dimethyl-2-iso*propylthiazolidine-2-carboxylic-3-glyoxylic anhydride (form* A) (Found: C, 49·4; H, 5·5; N, 4·4; S, 10·4. $C_{13}H_{17}O_6NS$ requires C, 49·5; H, 5·4; N, 4·4; S, 10·2%).

Form *B* of the thiazolidine-acid (1 g.) in dry dioxan (10 c.c.) was treated similarly with oxalyl chloride (1 c.c.), to yield *form* B of the *anhydride*, which was sublimed in a high vacuum and crystallised from dry xylene and dry ether–pentane to afford slender rods, m. p. 139° (Found: C, 49·6; H, 5·5. $C_{13}H_{17}O_6NS$ requires C, 49·5; H, 5·4%). A mixture of the anhydrides *A* and *B* had m. p. *ca.* 120°.

Reaction Products of the Anhydrides.—(*a*) The anhydride *A* (200 mg.) was treated with ethanol (5 c.c.) and after 16 hours the solution was distilled with water. *Form* A of *4-carbomethoxy-3-ethoxalyl-5 : 5-dimethyl-2-iso*propylthiazolidine-2-carboxylic acid* crystallised from ethanol–water in prisms, m. p. 178° (decomp.) (Found: C, 50·4; H, 6·5; N, 3·9. $C_{15}H_{23}O_7NS$ requires C, 49·9; H, 6·4; N, 3·9%). Treatment of this compound with ethereal diazomethane gave, on evaporation *in vacuo*, *form* A of *dimethyl 3-ethoxalyl-5 : 5-dimethyl-2-iso*propylthiazolidine-2 : 4-dicarboxylate* which crystallised from methanol–water in compact prisms, m. p. 141° (Found: C, 51·3; H, 6·8. $C_{16}H_{25}O_7NS$ requires C, 51·2; H, 6·7%). Form *A* of 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (0·3 g.),

dissolved in dry chloroform (10 c.c.) containing pyridine (0·2 c.c.), was treated with ethoxalyl chloride (0·16 c.c.). After 4·5 hours at room temperature the solution was extracted with aqueous sodium hydrogen carbonate. The aqueous extract was washed with ether, acidified, and re-extracted with ether, evaporation of which yielded form *A* of 4-carbomethoxy-3-ethoxalyl-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid, m. p. 175—178°, converted by ethereal diazomethane into the 2 : 4-dicarbomethoxy-compound, m. p. 138—139°, which did not depress the m. p. of the material described above. Interaction of the anhydride *A* (0·4 g.) with dry methanol (2 c.c.) afforded *4-carbomethoxy-3-methoxalyl-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acid*, m. p. 195° (decomp.), unaltered by recrystallisation from methanol–water (Found: C, 48·4; H, 6·0; N, 4·2. $C_{14}H_{21}O_7NS$ requires C, 48·4; H, 6·0; N, 4·0%). Esterification with diazomethane in ether gave a product no longer soluble in aqueous sodium hydrogen carbonate: *dimethyl 3-methoxalyl-5 : 5-dimethyl-2-isopropylthiazolidine-2 : 4-dicarboxylate* separated from methanol–water in prisms, m. p. 116—117° (Found: C, 50·0; H, 6·5; N, 4·3. $C_{15}H_{23}O_7NS$ requires C, 49·9; H, 6·4; N, 3·9%). The anhydride *A* (100 mg.) was set aside with water (several drops) for 16 hours, and the resulting material recrystallised from ethyl acetate–light petroleum (or ether–pentane) to form elongated prisms, m. p. 149° (decomp.), of *form* A of *4-carbomethoxy-3-oxalo-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acid* (Found: C, 46·5; H, 6·0; N, 4·3. $C_{13}H_{19}O_7NS$ requires C, 46·8; H, 5·7; N, 4·2%). Treatment of this di-acid with ethereal diazomethane provided the 2 : 4-dicarbomethoxy-3-methoxalyl compound, identical with that already described. The anhydride *A* was kept at room temperature for 16 hours with 2 : 4-dinitrophenylhydrazine in dry dioxan. Water and chloroform were then added, the mixture was shaken, and the chloroform layer separated and extracted with aqueous sodium hydrogen carbonate. Acidification of the reddish extract, followed by re-extraction with chloroform and evaporation of that solvent, afforded a gum which crystallised under ether–light petroleum. From ethanol–water, pale yellow hexagonal plates, m. p. 195° (decomp.), of the dinitrophenylhydrazide, probably *2-carboxy-4-carbomethoxy-5 : 5-dimethyl-2-isopropylthiazolidine-3-glyoxalo-2′ : 4′-dinitrophenylhydrazide*, crystallised (Found: C, 44·1; H, 4·6; N, 13·3. $C_{19}H_{22}O_{10}N_5S$ requires C, 44·4; H, 4·5; N, 13·6%). Anhydride *A* (100 mg.) was treated with benzylamine, a vigorous reaction taking place. Chloroform (15 c.c.) was added and the solution was washed with dilute hydrochloric acid, water, and aqueous sodium hydrogen carbonate. The alkaline extract was filtered, chilled in ice, and acidified. A white solid separated, soluble in ammonium hydrogen carbonate with effervescence. Several crystallisations from ethanol gave the benzylamide (most likely *2-carboxy-4-carbomethoxy-5 : 5-dimethyl-2-isopropylthiazolidine-3-glyoxalobenzylamide*) as feathery needles, m. p. 163—164° (decomp.) (Found: C, 56·0; H, 6·5. $C_{20}H_{24}O_6N_2S$ requires C, 56·9; H, 6·2%). By treating the anhydride *A* with benzylamine and, when evolution of heat had ceased, dissolving the gum in ethanol and adding dilute hydrochloric acid almost to turbidity, a different *benzylamine* derivative, possibly (VI), separated; it was insoluble in dilute acid and alkali and crystallised from ethanol–water in prismatic needles, m. p. 189° (decomp.) (Found: C, 62·7; H, 6·4; N, 7·8. $C_{18}H_{22}O_3N_2S$ requires C, 62·4; H, 6·4; N, 8·1%).

(*b*) In ethanol, anhydride *B* dissolved to form *4-carbomethoxy-3-ethoxalyl-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acid* (*form* B) which separated from ethanol–water in clusters of plates, m. p. 126° (Found: C, 50·3; H, 6·3; N, 4·3. $C_{15}H_{23}O_7NS$ requires C, 49·9; H, 6·4; N, 3·9%). The identical thiazolidine (mixed m. p. undepressed) was produced by acylating form *B* of 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (0·3 g.) with ethoxalyl chloride (0·16 c.c.) in dry chloroform (10 c.c.) containing pyridine (0·2 c.c.). With water, anhydride *B* afforded *4-carbomethoxy-3-oxalo-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acid* (*form* B) which crystallised from ether–pentane in prisms, m. p. 135—136° (decomp.) (Found: C, 47·1; H, 6·0; N, 4·6. $C_{13}H_{19}O_7NS$ requires C, 46·8; H, 5·7; N, 4·2%). Benzylamine reacted vigorously with anhydride *B* to form a neutral derivative which separated from ethanol–water in prisms, m. p. 186° (decomp.) (Found: C, 62·8; H, 6·3; N, 7·7%), apparently identical with the material (see above) from anhydride *A*.

Thermal Behaviour of Certain Thiazolidines and the Oxalo-anhydrides.—4-Carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (form *A*) (1 g.) was heated under reflux in pure dry ψ-cumene (20 c.c.) for 50 minutes. 0·64 Mol.-equiv. of a gas was evolved, completely absorbed by concentrated potassium hydroxide solution. The ψ-cumene was distilled off *in vacuo*, and the residue treated with ethereal hydrogen chloride. From chloroform–ether a pure stereoisomer of *methyl 5 : 5-dimethyl-2-isopropylthiazolidine-4-carboxylate hydrochloride* (0·7 g.) crystallised as clusters of prisms, m. p. 180° (decomp.) (Found: N, 5·6. $C_{10}H_{20}O_2NClS$ requires N, 5·5%). The same compound, m. p. 180° (decomp.) (mixed m. p. 180°) was similarly obtained from form *B* of the thiazolidine-2-carboxylic acid. Treatment of the decarboxylation product (0·5 g.) with hot 10% mercuric chloride in methanol (10 c.c.), followed by addition of aqueous 5% mercuric chloride (10 c.c.) and water (80 c.c.), yielded a white precipitate (1 g.), m. p. *ca.* 110°, the filtrate from which with 2 : 4-dinitrophenylhydrazine in dilute hydrochloric acid afforded pale orange laths of the derivative of *iso*butyraldehyde, m. p. 182° (not depressed in admixture with an authentic specimen). The white precipitate was dissolved in moist ethyl acetate and decomposed with hydrogen sulphide. Mercuric sulphide was filtered off and the ethyl acetate evaporated *in vacuo*, to leave a residue of needle-shaped crystals, m. p. 170°, recognised as the hydrochloride of penicillamine methyl ester by mixed m. p. determination and ferric chloride colour (purple in dilute aqueous sodium hydrogen carbonate).

Penicillamine methyl ester hydrochloride (1 g.) was stirred with *iso*butyraldehyde (1 c.c.), whereupon the mixture became warm and syrupy and then set to a solid (1·3 g.), m. p. 162—164°, which was washed with ether and recrystallised several times from chloroform–ether. *Methyl 5 : 5-dimethyl-2-isopropylthiazolidine-4-carboxylate hydrochloride* formed prisms, m. p. 167° (decomp.) (C, 47·0; H, 7·7; N, 5·4. $C_{10}H_{20}O_2NClS$ requires C, 47·2; H, 7·9; N, 5·5%). This hydrochloride (1 g.) was made alkaline with aqueous sodium hydrogen carbonate, the oil extracted with chloroform, and the oil obtained on evaporating the chloroform solution was heated under reflux in ψ-cumene (10 c.c.) for 1 hour. After removal of the solvent *in vacuo* and addition of ethereal hydrogen chloride, the high-melting form of the thiazolidine hydrochloride was obtained (mixed m. p. undepressed). Form *A* of 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (2 g.) in pyridine (25 c.c.) was treated with

acetyl chloride (1 c.c.). After 1·5 hours, excess of pyridine was removed *in vacuo*, and the residue dissolved in chloroform (50 c.c.). The solution was washed with dilute hydrochloric acid and water and evaporated, and the residue treated with ether. *4-Carbomethoxy-3-acetyl-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acid* (1·3 g.) formed prisms, m. p. 152°, from ethyl acetate–light petroleum (Found : C, 51·9; H, 6·8. $C_{13}H_{21}O_5NS$ requires C, 51·5; H, 6·9%), and reacted with diazomethane to give *dimethyl 3-acetyl-5 : 5-dimethylisopropylthiazolidine-2 : 4-dicarboxylate* (1 g.) which crystallised from methanol–water as prisms, m. p. 100° (Found : C, 52·4; H, 7·1; N, 4·4. $C_{14}H_{23}O_5NS$ requires C, 53·0; H, 7·3; N, 4·4%). The diester (0·7 g.) was recovered unchanged (m. p. and mixed m. p. 99—100°) after being heated under reflux in ψ-cumene (10 c.c.) for 1 hour. Portions of 4-carbomethoxy-3-oxalo-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (form *A*) (2 × 0·1 g.) were heated at 150°, and heated under reflux in dry xylene, till gas evolution ceased, after which (by evaporation in the case of the xylene experiment, and crystallisation from ethanol–water) form *A* of 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid was obtained as plates, m. p. 180—181°, undepressed when mixed with an authentic specimen. 4-Carbomethoxy-3-oxalo-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (form *A*) (0·7 g.) in methanol was added to a hot 10% solution of mercuric chloride in 1 : 1 aqueous methanol (20 c.c.), whereupon gas was slowly evolved. After several days the mixture was diluted with water (80 c.c.), and the white precipitate collected. The filtrate afforded the 2 : 4-dinitrophenylhydrazone of α-keto*iso*butyric acid as pale yellow laths (0·2 g.), m. p. 189—190° (undepressed on admixture with authentic material, m. p. 195°), which crystallised from ethanol–water or benzene (Found : C, 44·9; H, 4·6; N, 19·0. Calc. for $C_{11}H_{12}O_6N_4$: C, 44·6; H, 4·1; N, 18·9%). Rimington (*Onderstepoort J. Vet. Sci.*, 1935, **5**, 445) gives m. p. 189—191°. From the mercuric chloride precipitate, penicillamine methyl ester hydrochloride, m. p. 170°, was recovered as previously described.

The anhydride (form *A*) (200 mg.) in pyridine (5 c.c.) was heated on the steam-bath for 2 hours. Excess of pyridine was evaporated *in vacuo*, and the residue dissolved in chloroform. After extraction with aqueous hydrochloric acid and then sodium hydrogen carbonate, the chloroform was removed *in vacuo* to yield a trace of neutral material which, when washed with ether, afforded an unidentified yellow solid, m. p. 65—70° (decomp.). Acidification of the hydrogen carbonate extract precipitated a gum; this slowly solidified and from ethanol–water crystallised as thin laths, m. p. 180—181° (decomp.) (Found : C, 50·3; H, 7·5; N, 5·6. Calc. for $C_{11}H_{19}O_4NS$: C, 50·6; H, 7·3; N, 5·4%), which did not depress the m. p. of 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (form *A*). The same thiazolidine was similarly obtained after heating the anhydride (form *A*) (200 mg.) under reflux in xylene (10 c.c.) containing quinoline (0·5 c.c.) for 1·5 hours, and also after heating a mixture of the anhydride *A* (350 mg.) and powdered glass (from two 5 × ⅝″ test tubes) at 150—160° for 2 hours. The anhydride *A* (150 mg.) was mixed with a moderately large excess of thoria and heated at 110° in a high vacuum. Slightly impure anhydride *A* sublimed as prisms, m. p. 118—120° (decomp.) (Found : C, 49·6; H, 5·8. Calc. for $C_{13}H_{17}O_6NS$: C, 49·5; H, 5·4%). The sublimate and thoria were recombined and heated at 130—140° under atmospheric pressure for 1 hour. On evacuation of the vessel, a crystalline sublimate formed which was acidic and readily soluble in ether. The anhydride (form *A*) (1 g.), mixed with powdered glass (previously maintained at 190° *in vacuo*), was heated at 150—160° for 1·5 hours, moisture being excluded by a calcium chloride tube. The product was extracted from the powdered glass with chloroform, and the solution passed through a column of alumina to yield, on evaporation of the eluate, a neutral brown oil, possibly impure *methyl 3-formyl-5 : 5-dimethyl-2-isopropylthiazolidine-4-carboxylate* (Found : C, 53·95; H, 7·7; N, 5·3. $C_{11}H_{19}O_3NS$ requires C, 53·9; H, 7·8; N, 5·7%). An attempt to prepare authentic material by slowly treating a mixture of methyl 5 : 5-dimethyl-2-*iso*propylthiazolidine-4-carboxylate hydrochloride (1 g.), sodium formate (350 mg.), and anhydrous formic acid (10 c.c.) with acetic anhydride (5 c.c.) led to the isolation of a neutral oil which could not be induced to crystallise. In other experiments, the anhydride *A* was heated at 150—160° with dried powdered glass in a current of purified dried nitrogen, and the evolved carbon dioxide (0·38 and 0·54 mol. on different occasions) determined. By the procedure previously described an oil was isolated (Found : C, 53·0; H, 7·5; N, 5·8%). This was heated with mercuric chloride (2 g.) in methanol (20 c.c.) for 30 minutes, water was added, and the filtrate treated with the dinitrophenylhydrazine reagent. A pale yellow derivative separated which crystallised from ethanol as laths, m. p. 179° alone or on admixture with the 2 : 4-*dinitrophenylhydrazone* (yellow laths, m. p. 178°, from methanol) of methyl α-keto*iso*butyrate (Found : C, 46·9; H, 4·7; N, 17·8. $C_{12}H_{14}O_6N_4$ requires C, 46·45; H, 4·5; N, 18·1%) which was prepared (*a*) from α-keto*iso*butyric acid methylated with diazomethane and (*b*) by a similar esterification of the acid 2 : 4-dinitrophenylhydrazone. The oily product from a further experiment with powdered glass was not chromatographed; the oil crystallised partly almost at once, and the solid of m. p. 128—130° (decomp.) was shown to consist substantially of unchanged anhydride *A* by interaction with ethanol to give 4-carbomethoxy-3-ethoxalyl-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid, m. p. 178—179° (Found : C, 49·9; H, 6·3; N, 3·7. Calc. for $C_{15}H_{23}O_7NS$: C, 49·9; H, 6·4; N, 3·9%), by interaction with benzylamine to give material (Found : C, 63·0; H, 6·5. Calc. for $C_{18}H_{23}O_3N_2S$: C, 62·4; H, 6·4%) of m. p. 186—188° alone or on admixture with the neutral benzylamine derivative previously described, and by formation, on exposure to atmospheric moisture, of an acid which was shown to be 4-carbomethoxy-3-oxalo-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid by reaction with diazomethane to give the 2 : 4-dicarbomethoxy-3-methoxalyl derivative, m. p. 115—117°. Treatment of the remaining recovered anhydride with hot methanolic mercuric chloride led, by a method already outlined, to isolation of α-keto*iso*butyric acid 2 : 4-dinitrophenylhydrazone identified by its m. p. and mixed m. p.

The oxalo-anhydride *A*, freshly prepared from 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (2·08 g.) and oxalyl chloride (2 c.c.) in dry dioxan (20 c.c.), was redissolved in dioxan (10 c.c.), and the solution added to rigorously dried thorium oxide (11 g.). After mixing, the solvent was removed at 60° *in vacuo*, and the residual mixture heated at 145—150° for 2 hours; 1·05 mols. of gas (155 c.c. at N.T.P.) were evolved which consisted of carbon dioxide (52%) and monoxide (48%). The thoria was extracted with chloroform and the extract evaporated, whereupon

crystals separated. Recrystallisation from xylene afforded prismatic needles, m. p. 135—136°, identified as form *A* of the anhydride by mixed m. p. determination and also by interaction with ethanol to give the 3-ethoxalylthiazolidine, m. p. 174—176° (decomp.). Extraction of the non-crystalline material, obtained from the chloroform, with aqueous sodium hydrogen carbonate left a (neutral) oil from which no solid derivative resulted. Acidification of the alkaline solution and extraction with ether also afforded an oil which, however, yielded a salt with ethereal benzylamine. From methanol–ether, the *bisbenzylamine* salt of 4-carbomethoxy-3-oxalo-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid formed small needles, m. p. 171—172° (Found : C, 59·1; H, 6·8; N, 7·7. $C_{27}H_{37}O_7N_3S$ requires C, 59·2; H, 6·8; N, 7·7%). When regenerated from this salt the di-acid crystallised and with diazomethane in ether gave the known dimethyl 3-methoxalyl-5 : 5-dimethyl-2-*iso*propylthiazolidine-2 : 4-dicarboxylate (form A).

Form *A* of the anhydride, prepared in the usual fashion from 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (4 g.) and oxalyl chloride (2·5 c.c.) in dioxan (30 c.c.) but in a flask containing dried powdered glass, was heated at 130—140° for 3 hours. Extraction of the mixture with chloroform afforded a brown oil (3·7 g.) which had a camphor-like odour. The oil was repeatedly extracted with boiling light petroleum, and the extract distilled in a high vacuum to give an almost colourless neutral oil, b. p. 80°/10^{-4} mm. (Found : C, 52·6; H, 7·3; N, 7·05; S, 11·5%). The oil afforded a flocculent yellow derivative with the 2 : 4-dinitrophenylhydrazine reagent. This failed to crystallise from benzene–light petroleum or ethanol–water, and chromatography in benzene on alumina gave only a resin. The gummy residue from the foregoing distillation on being heated to 120° in a high vacuum yielded a solid sublimate. This crystallised from ether–pentane in flattened prisms (Found : C, 49·5; H, 6·7%), m. p. 178—179° alone or on admixture with *4-carbomethoxy-3-formyl-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acid* (m. p. 183—184°, from chloroform–pentane) (Found : C, 49·5; H, 6·4. $C_{13}H_{19}O_5NS$ requires C, 49·8; H, 6·6%) which was prepared by treating 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (1 g.) in cold anhydrous formic acid (10 c.c.) with acetic anhydride (5 c.c.), added dropwise.

Grateful acknowledgment is made of the award of a Beit Scientific Research Fellowship (to J. A. E.), and of assistance from the Therapeutic Research Corporation of Great Britain, Ltd. Sir Ian Heilbron, D.S.O., F.R.S., is thanked for his close interest in this work.

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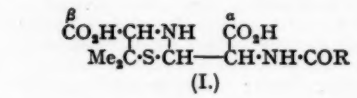
500. *Syntheses in the Penicillin Field. Part III. The Preparation of Model Thiazolines and Thiazoles.*

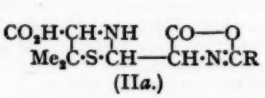
By A. H. Cook and J. A. Elvidge.

A projected route to penicillins from thiazolines is outlined. Useful intermediates of the thiazoline series from acylamidomalonic and acylamidocyanoacetic esters were sought unsuccessfully, although corresponding members of the thiazole series were obtained and studied.

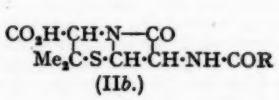
It was early recognised that cyclodehydration of penicilloic acids (I) provided a possible route to synthetic penicillins irrespective of the uncertainty then prevailing concerning the correct structure of the natural antibiotics; clearly each of the favoured representations, (II*a*) and (II*b*), is potentially so derivable. Treatment of penicilloic derivatives with various dehydrating agents was found indeed to afford weak, often transitory, antibacterial activities, but it soon became clear that the difficulties inherent in this direct approach were so formidable as to preclude its eventual usefulness. Consequently, it was decided to investigate the preparation and cyclisation of thiazoline analogues of the penicilloates, namely the dehydropenicilloates (III). The possibility was foreseen that the α-carboxyl group of these compounds might prove sufficiently stable for azlactonisation to be effected in the normal manner. Alternatively it appeared that cyclisation of the α-esters to thiazolinyl-alkoxyoxazoles (IV) might be feasible, and that thiazolinyl-oxazolones (V) might be thence obtained by replacing appropriate substituents R′ by H. In either event the product was to have been reduced to the thiazolidinyl-oxazolone (II*a*) which might well have isomerised to the β-lactam structure (II*b*) by internal self-acylation.



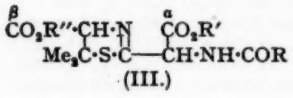
(I.)



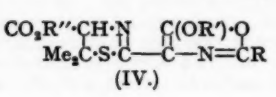
(II*a*.)



(II*b*.)



(III.)



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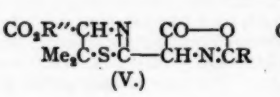

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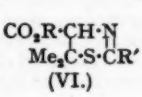


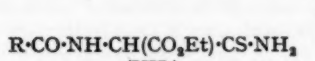
(VI.)

In this paper the results are recorded of initial experiments directed towards these objectives (further work along these lines is described in " The Chemistry of Penicillin," Princeton Univ. Press, 1949, Chap. XXII, and in later Parts of this Series). First, it was necessary to study methods for preparing Δ^2-thiazolines derived from penicillamine, and secondly it had to be demonstrated that reduction of such thiazolines to the corresponding thiazolidines could be effected under mild conditions.

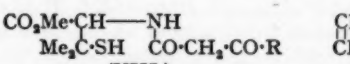
Cyclodehydration of *N*-acylpenicillamines constituted the first example of the preparation of thiazolines from penicillamine (Merck, *M.* 35; *op. cit.*, p. 470). Another method, discovered at almost the same time, consisted in heating penicillamine ethyl ester hydrochloride with thioacetamide whereby hydrogen sulphide was evolved, ammonium chloride separated, and ethyl 2 : 5 : 5-trimethylthiazoline-4-carboxylate (VI; R = Et, R′ = Me) was isolated as an oil characterised as its hydrochloride (Bentley, Catch, Cook, Heilbron, and Shaw, *CPS.* 267; *op. cit.*, p. 938). The same compound was obtained under similar conditions, though less conveniently, by use of acetonitrile in place of thioacetamide. These procedures did not seem generally applicable, however, the analogous reaction with thiobenzamide, for example, not being achieved. Moreover attempts to condense penicillamine methyl ester hydrochloride with *phenylacetamidocarbethoxythioacetamide* (VII; R = CH_2Ph) resulted only in formation of an unidentified substance which was also obtained by the action of heat on the thioamide alone. This thioamide and the n-*hexoamido*-analogue (VII; R = *n*-C_5H_{11}) were prepared from the corresponding phenylacet- and *n*-hexo-amidocarbethoxyacetonitrile which in turn were obtained (*idem*, *op. cit.*, pp. 725, 727) by reducing ethyl oximinocyanoacetate to the hitherto unknown ethyl aminocyanoacetate, followed by acylation with the appropriate acid chlorides.

It was then found that the condensations with penicillamine derivatives to yield thiazolines could be extended to ethyl malonate (Cook, Elvidge, Heilbron, and Levy, *CPS.* 443; *op. cit.*, p. 885). Thus when the latter ester was heated with penicillamine methyl ester a mixture of methyl 5 : 5-dimethyl-2-carbethoxymethylthiazoline-4-carboxylate (VI; R = Me, R′ = $CH_2{\cdot}CO_2Et$) and the acylpenicillamine (VIII; R = OEt) resulted, the latter being characterised as the N-*malonamyl* derivative (VIII; R = NH_2). An attempted condensation of penicillamine methyl ester with hexoamidomalonic ester, however, did not yield a thiazoline (dehydropenicilloate) useful for penicillin synthesis.

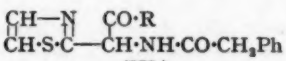
Before real progress in synthesising penicillins *via* thiazolines could be made a method of reducing the thiazoline ring system to the corresponding thiazolidine system had to be found. The first example of such a reduction was afforded by the conversion of the above ethyl 2 : 5 : 5-trimethylthiazoline-4-carboxylate (VI; R = Et, R′ = Me) to the corresponding thiazolidine by means of an excess of aluminium amalgam in moist ether. The product was characterised as a thiazolidine by means of its crystalline hydrochloride and by scission with mercuric chloride to yield acetaldehyde, isolated as its 2 : 4-dinitrophenylhydrazone (Bentley, Catch, Cook, Heilbron, and Shaw, *loc. cit.*) Several examples of this type of reduction were later encountered (cf. Parts VII and VIII of this Series, to be published) and of particular interest was the reduction of the " dehydropenilloate " (VI; R = Me, R′ = $CH_2{\cdot}NH{\cdot}CO{\cdot}CH_2Ph$) (Barltrop, Abraham, Baker, Chain, and Robinson, *CPS.* 463; *op. cit.*, p. 938). The fact that thiazolines could be reduced with neutral aluminium amalgam made the approach to penicillins *via* thiazolines attractive, since penicillins are stable to this reagent and were indeed purified by its action in earlier work on the natural penicillins obtained from *P. notatum* (see Abraham and Chain, *Brit. J. Exp. Path.*, 1942, **23**, 103).



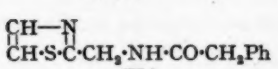
(VII.)



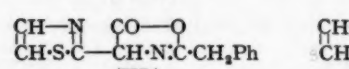
(VIII.)



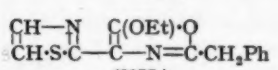
(IX.)



(X.)



(XI.)



(XII.)

The failure of (VII; R = CH_2Ph) to condense with penicillamine methyl ester to yield a thiazoline prompted closer investigation of its nature and, in particular, of its reaction with α-halogeno-carbonyl compounds. In the manner characteristic of thioamides, (VII; R = CH_2Ph) condensed with diethyl bromoacetal to yield a thiazole (IX; R = OEt), isolated as the free *base* and the *hydrobromide hydrate*.

Since (IX; R = OEt) was readily obtainable and in view of the known stability of the thiazole ring system and the absence of reactive groups in (IX) other than those appertaining

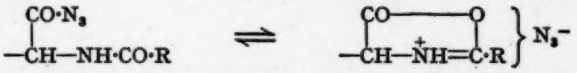
to the α-acylamido-acid portion of the molecule, it was decided to utilise it for studying certain possible methods of synthesising oxazolones, in particular (XI). The methods studied comprised (*a*) dehydration of the acid (IX; R = OH) (*b*) thermal elimination of hydrazoic acid from the azide (IX; R = N_3), and (*c*) cyclisation of the acylamido-esters (IX; R = OEt or O·CHPh$_2$) with phosphorus pentachloride.

(IX; R = OEt) was hydrolysed readily by aqueous sodium hydroxide to give the *acid* (IX; R = OH) which, when pure, appeared to be stable at ordinary temperatures. The crude acid, however, lost carbon dioxide slowly in the solid state or very rapidly in chloroform solution, to afford the *compound* (X), also obtained on heating the acid to its melting point. It was not surpising, therefore, that treatment of (IX; R = OH) with acetic anhydride also gave (X), and other attempts to azlactonise the acid by using acetic anhydride in pyridine or by the action of acetic anhydride, with and without pyridine, on the sodium salt (IX; R = ONa) were likewise unsucessful. The instability of the acid (IX; R = OH) resembled that of the penicilloic acids (I) (containing a thiazolidine instead of a thiazole ring), and it seemed unlikely that related acids of the thiazoline series would prove sufficiently stable for normal azlactonisation to be achieved. This was later confirmed since 5 : 5-dimethyl-2-*p*-nitrobenzamidocarboxymethylthiazoline-4-carboxylic acid (VI; R = H, R′ = CH(CO$_2$H)·NH·CO·C$_6$H$_4$·NO$_2$) could not be isolated after hydrolysis of methyl 5 : 5-dimethyl-2-*p*-nitrobenzamidocarbethoxymethylthiazoline-4-carboxylate, the only isolable product being the dehydropenilloate analogue (VI; R = H, R′ = CH$_2$·NH·CO·C$_6$H$_4$·NO$_2$) (Cook, Elvidge, and Heilbron, *CPS.* 680; *op. cit.*, p. 886).

The acid (IX; R = OH) was therefore treated with diazomethane to yield a crude *ester* (IX; R = OMe) from which the crystalline *hydrazide* (IX; R = NH·NH$_2$) was prepared. The latter compound was also obtained from (IX; R = OEt) and hydrazine hydrate. With nitrous acid the hydrazide yielded the *azide* (IX; R = N_3). In benzene at 60° it evolved gas steadily and a product was isolated which was unexpectedly found to be the *amide* (IX; R = NH_2), identified with an authentic specimen prepared from (IX; R = OEt) and ammonia. Further attempts to prepare the oxazolone (XI) by eliminating the elements of hydrazoic acid from (IX; R = N_3) similarly failed. Only the amide (IX; R = NH_2) was isolated after treating the azide with acetic anhydride in dimethylaniline, acetic anhydride alone, dry pyridine, or dimethylaniline at 70°, or by shaking it in benzene with excess of silver oxide. The unusual transformation of the azide (IX; R = N_3) into the amide (IX; R = NH_2), thus observed under a variety of conditions, may be explained by assuming that the azide was hydrated. Water of hydration may be loosely associated, ·CH·CON$_3$,H$_2$O, or it may be bound in more intimate fashion as in the equivalent structures, ·CH·CO·NH·NH·NO and ·CH·CO·NH·N:N·OH. In each case formation of the amide could occur through loss of nitrous oxide (N_2O). A similar transformation was observed by Thompson and Wolfrom (*J. Amer. Chem. Soc.*, 1946, **68**, 1509), while a less close analogy is offered by the reaction undergone by certain disubstituted hydrazines with nitrous acid in producing amines by the loss of nitrous oxide from an unstable intermediate:

$$RR'N\cdot NH_2 \longrightarrow RR'N\cdot NH\cdot NO \longrightarrow RR'NH + N_2O$$

Whatever the actual mechanism of the above change or the precise structure of the compound (IX; R = N_3), its essentially acid-azide nature was clearly demonstrated by the reaction with benzylamine. Benzylammonium azide was formed together with the *benzylamide* (IX; R = NH·CH$_2$Ph), also obtained from (IX; R = OEt) and benzylamine. Thus the azide (IX; R = N_3) behaved in this reaction like an acid halide, acting as an acylating agent. The reaction with benzylamine could also be explained, however, by assuming the azide to be in reality an oxazolone hydrazoide, but the result of the experiments with pyridine, dimethylaniline, and silver oxide did not reveal any oxazolone character as indicated by the scheme:



There existed little hope, therefore, of converting related α-acylamido-acid azides, which could no doubt have been prepared in the thiazoline series, into the oxazolones. Nevertheless, the method succeeded admirably in a simple case, for hippuric acid azide afforded a 90% yield of 2-phenyloxazolone when warmed in chloroform solution.

In an attempt to prepare oxazolones by the third method, (*c*), the thiazole ester (IX; R = OEt) was heated with phosphorus pentachloride, whereupon cyclodehydration occurred,

to yield the crystalline *5-ethoxy-4-2'-thiazolyl-2-benzyloxazole* (XII). The ester (IX; R = OEt) was not changed by heating it with the possible alternative cyclising reagents, acetic anhydride and fused sodium acetate. Since (XII) represented a stable end-product from which the thiazolyl-oxazolone could not be obtained, the *benzhydryl* ester (IX; R = O·CHPh$_2$) was prepared from (IX; R = OH) and diazodiphenylmethane and treated with phosphorus pentachloride; it was hoped that the 5-benzhydryloxy-oxazole would have resulted and this compound might well have undergone hydrogenolysis to the required oxazolone. Unfortunately however, a stable phosphorus chloride *complex* resulted on attempted cyclisation.

Further experiments with these thiazoles were discontinued but the experience gained was applied to the solution of problems encountered in the thiazoline series (cf. Parts V, VII, and VIII of this Series, to be published).

Experimental.

Acylamidocarbethoxythioacetamides.—Ethanol (600 c.c.), in which sodium (1 g.) had been dissolved, was cooled to −10° and saturated with dry hydrogen sulphide. Ethyl phenylacetamidocyanoacetate (57·7 g.) (*op. cit.*) was then added and the mixture heated overnight in a sealed vessel at 50—60°. The solution was evaporated to small bulk *in vacuo*, the residue was dissolved in chloroform, and the solution washed with water. Evaporation gave a white product (44 g.), m. p. 112—115°. From chloroform–light petroleum, *phenylacetamidocarbethoxythioacetamide* crystallised as clusters of flattened needles, m. p. 114—115° (Found: C, 56·1; H, 5·7; N, 9·7. $C_{13}H_{16}O_3N_2S$ requires C, 55·7; H, 5·7; N, 10·0%). The compound was readily soluble in dilute aqueous sodium hydroxide. *n-Hexoamidocarbethoxythioacetamide*, prepared similarly from ethyl *n*-hexoamidocyanoacetate (1·2 g.) and a saturated solution of hydrogen sulphide in ethanol (25 c.c.) containing dissolved sodium (25 g.), crystallised from ether–light petroleum in prisms (0·7 g.), m. p. 83° (Found: C, 50·8; H, 7·6; N, 10·5. $C_{11}H_{20}O_3N_2S$ requires C, 50·8; H, 7·7; N, 10·8%).

Preparation of Thiazolines.—DL-Penicillamine ethyl ester hydrochloride, when heated with thioacetamide, gave ethyl 2 : 5 : 5-trimethylthiazoline-4-carboxylate and thence the hydrochloride. The latter product could not be reduced catalytically with Adams's catalyst or with palladium on polyvinyl alcohol, but the base was successfully reduced with aluminium amalgam to the corresponding thiazolidine in 60% yield (*op. cit.*, p. 938).

Penicillamine methyl ester, prepared by treating the hydrochloride (2 g.) with aqueous sodium hydrogen carbonate and extracting the mixture with chloroform, was heated with phenylacetamidocarbethoxythioacetamide (2·7 g.) at 170° for 30 minutes, whereupon ammonia and hydrogen sulphide were evolved. The reaction product was dissolved in chloroform, and the solution was extracted with 3·5% hydrochloric acid (6 × 20 c.c.), washed with water (3 × 20 c.c.), and chromatographed on magnesium oxide (column, 20 × 1 cm.). A pale red zone moved down the column, followed by a darker and broader band. The eluate from the latter, when evaporated and treated with ether, deposited a little red crystalline material, m. p. 190—192°. By rendering the hydrochloric acid extract alkaline with ammonia and back-extracting the turbid solution with chloroform, a further quantity of the *substance*, m. p. 192°, resulted (total yield, 0·3 g.); it formed pale pink prisms from chloroform (charcoal) on addition of ether and light petroleum (Found: C, 62·2; H, 6·0; N, 16·3%). The same substance arose in small yield by heating phenylacetamidocarbethoxythioacetamide alone at 170—200° for 30 minutes.

The base from penicillamine methyl ester hydrochloride (2 g.) was heated at 170° with ethyl hexoamidomalonate (3·7 g.) (Bentley, Catch, Cook, Elvidge, Heilbron, and Shaw, *CPS.* 63; *op. cit.*, p. 776). Effervescence occurred for some 8 minutes. The mixture was cooled and stirred with ether, and unchanged hexoamidomalonate (2·2 g.) collected. The ethereal filtrate was extracted with dilute hydrochloric acid, the extract was made alkaline with sodium hydrogen carbonate, and the resultant emulsion extracted with ether. From the ethereal layer the *styphnate* of penicillamine methyl ester disulphide was obtained; it crystallised from ethyl acetate–ether only after addition of a few drops of methanol; the solvated prisms had m. p. 71° (Found: C, 37·95, 38·1; H, 5·0, 5·3; N, 11·5. $C_{18}H_{27}O_{12}N_5S_2,CH_3·OH$ requires C, 37·9; H, 5·2; N, 11·65%).

Penicillamine methyl ester (from 4 g. of hydrochloride), mixed with ethyl malonate (5 c.c.), was added dropwise to ethyl malonate (10 c.c.) kept at 175°. After a further 10 minutes, the mixture was distilled (twice) under reduced pressure to yield an apparently homogeneous oil (2·5 g.), b. p. 156°/0·018 mm., which, however, was found to consist of a mixture of (VI; R = Me, R' = $CH_2·CO_2Et$) and (VIII; R = OEt) (Found: C, 48·9; H, 6·7; N, 5·4. $C_{11}H_{19}O_5NS$ requires C, 47·7; H, 6·9; N, 5·1. $C_{11}H_{17}O_4NS$ requires C, 51·0; H, 6·6; N, 5·4%). When kept at room temperature, the oil partly solidified. Recrystallisation of the solid from ethanol–water gave plates, m. p. 109—111°, of methyl 5 : 5-dimethyl-2-carbethoxymethylthiazoline-4-carboxylate (VI) (*op. cit.*, p. 885). Treatment of the remaining oily material with concentrated aqueous ammonia overnight afforded the *N-malonamyl* derivative (VIII; R = NH_2) of penicillamine methyl ester, which separated from ethanol or acetone–light petroleum as prisms, m. p. 107—108° (Found: C, 43·75; H, 6·6; N, 11·1. $C_9H_{16}O_4N_2S$ requires C, 43·6; H, 6·5; N, 11·3%).

Preparation of Thiazole Derivatives.—Phenylacetamidocarbethoxythioacetamide (5·6 g.), diethyl bromoacetal (4·2 g.) (Hartung and Adkins, *J. Amer. Chem. Soc.*, 1927, **49**, 2520), and alcohol (3 c.c.) were heated under gentle reflux for 1 hour, and the resulting dark syrup set aside to crystallise. The *2-phenylacetamidocarbethoxymethylthiazole hydrobromide* (3·5 g.) was washed with chloroform and recrystallised from chloroform–ether to form hydrated leaflets, m. p. 110—111° (frothing; with softening from 105°) (Found: C, 45·1; H, 4·8; N, 6·9. $C_{15}H_{17}O_3N_2BrS,H_2O$ requires C, 44·7; H, 4·7; N, 6·9%). Shaking a chloroform solution of this hydrobromide with aqueous sodium hydrogen carbonate afforded *2-phenylacetamidocarbethoxymethylthiazole*, which crystallised from ethanol–water as

feathery needles, m. p. 93° (Found: C, 59·0; H, 5·4; N, 9·2. $C_{13}H_{14}O_3N_2S$ requires C, 59·2; H, 5·6; N, 9·2%). Light absorption (ethanol): Max., 2420 A.; $E^{1\%}_{1\,cm.} = 220$.

A portion (987 mg.) of the preceding ester was shaken with 0·509N-sodium hydroxide (6·37 c.c.) for 15 minutes, and the filtered solution (diluted with water to 20 c.c.) was treated at 0° with 0·436N-hydrochloric acid (7·43 c.c.), whereupon a white solid (0·8 g.), m. p. 68—70° (vigorous frothing), separated. 2-*Phenylacetamidocarboxymethylthiazole*, purified by slow reprecipitation at 0° from sodium hydroxide solution (charcoal), formed small needles, m. p. 79° (vigorous frothing) (dried over phosphoric oxide at room temperature and pressure) (Found: C, 56·7; H, 4·6; N, 9·95. $C_{13}H_{12}O_3N_2S$ requires C, 56·5; H, 4·3; N, 10·15%). The resolidified melt had m. p. 98° alone or in admixture with the decarboxy-compound obtained by dissolving the thiazole-acid in cold chloroform, adding light petroleum, and cooling the mixture to 0°; *2-phenylacetamidomethylthiazole* formed plates, m. p. 98° (Found: C, 62·3; H, 5·5; N, 11·7. $C_{12}H_{12}ON_2S$ requires C, 62·1; H, 5·2; N, 12·1%). Whereas the dried purified thiazole acid, m. p. 79° (decomp.), appeared to be stable at room temperature (completely soluble in aqueous alkali after 120 hours), the crude acid slowly lost carbon dioxide: thus after 48 hours, a 400-mg. sample contained 215 mg. of material insoluble in alkali.

The remaining portion of 2-phenylacetamidocarboxymethylthiazole was treated with an excess of ethereal diazomethane, and the crude methyl ester heated with hydrazine hydrate (10 c.c.) in ethanol (5 c.c.) for 5 minutes on the steam-bath. Evaporation of the solution *in vacuo* left the *hydrazide* of 2-phenylacetamidocarboxymethylthiazole (0·6 g.), which crystallised from *iso*propanol as needles, m. p. 177° (Found: N, 19·7. $C_{13}H_{14}O_2N_4S$ requires N, 19·3%). A solution of the preceding hydrazide (325 mg.) in glacial acetic acid (5 c.c.) and 0·436N-hydrochloric acid (2·58 c.c.) was cooled to 0°, stirred, and treated dropwise during 15 minutes with sodium nitrite (90 mg.) in water (4 c.c.). After a further 15 minutes, ice-water (100 c.c.) was slowly added and the buff-coloured precipitate of the *azide* was collected, washed with water, and dried *in vacuo* over phosphoric oxide; yield, 210 mg.; m. p. 80—81° (decomp.). The azide (70 mg.) was treated with benzylamine (5 drops), whereupon heat was evolved and a solid separated. The latter, freed from red gum with 1 : 1 ethanol–ether, consisted of characteristic hexagonal plates of benzylammonium azide, identified with authentic material, m. p. 163° (decomp.), obtained from hydrazoic acid and benzylamine in ether. The red filtrate was warmed on the steam-bath for 20 minutes, and a second product precipitated from ethyl acetate by addition of ether. This material was identified with the *benzylamide* of 2-phenylacetamidocarboxymethylthiazole and formed groups of fine needles, m. p. 140°, from ethanol–light petroleum (or ill-formed laths from ethanol–water), obtained by boiling 2-phenylacetamidocarbethoxymethylthiazole (20 mg.) under reflux with benzylamine (2 drops) in ethanol (0·5 c.c.) for 30 minutes (Found: C, 65·3; H, 5·4. $C_{20}H_{19}O_2N_3S$ requires C, 65·75; H, 5·2%).

Azlactonisation Experiments.—(*a*) When freshly prepared phenylacetamidocarboxymethylthiazole was treated with cold acetic anhydride, it dissolved during 5—10 minutes with evolution of carbon dioxide. By evaporation *in vacuo*, an alkali-insoluble solid was obtained, recognised as 2-phenylacetamidomethylthiazole by mixed m. p. determination. A solution of 2-phenylacetamidocarboxymethylthiazole in dilute aqueous sodium hydroxide (1 equiv.) was lyophilised. The fluffy *sodium* salt (100 mg.) (freely water-soluble) was set aside for 16 hours with a cold mixture of acetic anhydride (2 c.c.) and dry pyridine (4 c.c.). Evaporation *in vacuo* then afforded a yellow gum, together with a small quantity of pale yellow needles, m. p. 89—90°, insoluble in aqueous sodium hydrogen carbonate. The m. p. was depressed to 73° when the *substance* was mixed with 2-phenylacetamidomethylthiazole. Attempts at purification gave only gums.

(*b*) The previously described thiazole azide (80 mg.) was heated in benzene at 60°. Gas was evolved and most of the solid passed into solution. On addition of light petroleum to the filtrate, a flocculent solid separated (Found: C, 56·8; H, 4·7; N, 15·5. $C_{13}H_{13}O_2N_3S$ requires C, 56·7; H, 4·7; N, 15·3%), which did not depress the m. p. of the authentic *amide* of 2-phenylacetamidocarboxymethylthiazole (long needles, m. p. 196°, from ethanol–water) prepared by heating 2-phenylacetamidocarbethoxymethylthiazole (20 mg.) in ethanol (1 c.c.) with concentrated aqueous ammonia (3 c.c.) for 10 minutes. The amide was also obtained from the acid azide in other ways, as already described.

Hippuric acid hydrazide (300 mg.) was dissolved in 2N-hydrochloric acid (3 c.c.), diluted with water (10 c.c.), and cooled to 0°. Sodium nitrite (150 mg.) in water (5 c.c.) was added dropwise, with stirring, and the white precipitate extracted into chloroform. The dried solution (Na_2SO_4) was treated with diazomethane, but there appeared to be no reaction. After 15 minutes, the solution was heated and evaporated to dryness *in vacuo*. The residual pale oil crystallised rapidly and the solid, washed with light petroleum (b. p. 60—80°), had m. p. 88—89° (yield: 230 mg., 92%). Recrystallised rapidly from ethanol, 2-phenyloxazolone had m. p. 91°; it was apparently formed on warming the hippuric azide.

(*c*) 2-Phenylacetamidocarbethoxymethylthiazole (1 g.) in chloroform (15 c.c.) (which had been shaken with phosphoric oxide) was treated with phosphorus pentachloride (2 g.), and the solution kept warm on the steam-bath for 1 hour. The liquid was shaken with excess of ice-cold aqueous sodium hydrogen carbonate, washed with water, dried (Na_2SO_4), and evaporated, to yield a brown gum which became a powdery solid (0·5 g.), m. p. 130—133°, on trituration with ether. Crystallisation from ethyl acetate (charcoal) by the addition of light petroleum afforded lustrous prismatic needles, m. p. 138°, of *5-ethoxy-4-2′-thiazolyl-2-benzyloxazole* (Found: C, 62·8; H, 4·9; N, 9·8. $C_{18}H_{14}O_2N_2S$ requires C, 62·9; H, 4·9; N, 9·8%). Light absorption (in ethanol): Max., 2780 A.; $E^{1\%}_{1\,cm.} = 770$. The material was soluble in concentrated hydrochloric acid. Freshly prepared 2-phenylacetamidocarboxymethylthiazole (1·5 g.) was treated overnight with an excess of ethereal diazodiphenylmethane (Staudinger, Anthes, and Pfenniger, *Ber.*, 1916, **49**, 1932). The acid did not dissolve but was slowly replaced by a deposit of the required ester (0·7 g.), m. p. 123° (from the filtrate 2-phenylacetamidomethylthiazole was precipitated by light petroleum; some decarboxylation of the starting material had therefore occurred). 2-[*Phenylacetamido*(*carbobenzhydryloxy*)*methyl*]*thiazole* (IX; R = $CHPh_2$) crystallised from chloroform–light petroleum as ragged-ended laths, m. p. 123° (Found: C, 70·55; H, 5·2; N, 6·5. $C_{26}H_{22}O_3N_2S$ requires C, 70·6; H, 5·0; N, 6·3%). The preceding ester (0·6 g.), phosphorus pentachloride (1·5 g.),

and dry chloroform (15 c.c.) were warmed together on the steam-bath for 1 hour. When the mixture was worked up as in the previous cyclisation experiment, a bluish-green crystalline residue resulted, m. p. 140—145°. This phosphorus chloride *complex* was firmly adsorbed on charcoal but on repeated crystallisation from chloroform–light petroleum pale yellow plates, m. p. 150° (to a red liquid), were eventually obtained (Found: C, 56·4; H, 3·3%).

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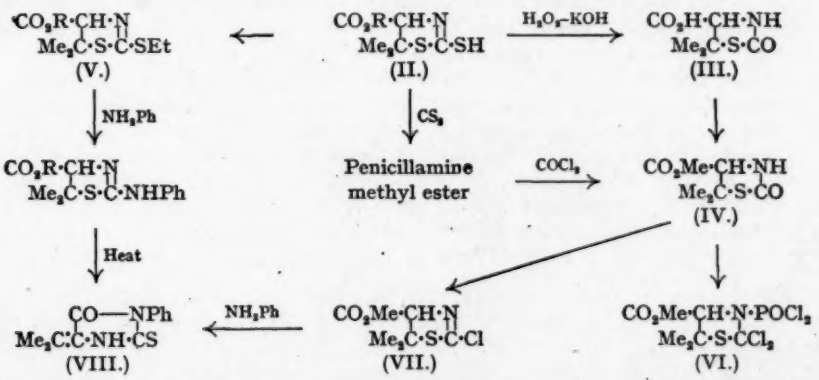
501. *Syntheses in the Penicillin Field. Part IV. Some 2-Substituted Thiazolines and their Reactivity.*

By A. H. COOK, J. A. ELVIDGE, and G. SHAW.

The 2-*mercaptothiazoline* (II; R = Me) was converted into *methyl* 5 : 5-*dimethylthiazolid*-2-*one*-4-*carboxylate* (IV) which was also obtained otherwise. Neither (II) nor (IV) condensed satisfactorily with representative compounds containing " reactive " methylene groups. Alkali-metal derivatives of the latter compounds failed also to react as expected with the 2-*chlorothiazoline* (VII) obtained from (IV), (VII) being converted into an iso*thiocyanate* regarded as (X). With aniline both (VII) and the 2-*ethylthio*-derivative (V) afforded 3-*phenyl*-5-iso*propylidene*-2-*thiohydantoin* (VIII).

DEHYDROPENICILLOATE derivatives (I) were required as intermediates in a projected synthesis of penicillins (see Parts III and V of this Series). In continued attempts to prepare such thiazolines the possibility was examined of condensing appropriate 2-substituted (*e.g.*, 2-mercapto- or 2-chloro-)thiazolines with suitable compounds having a reactive methylene group (*e.g.*, ethyl acylamidoacetates). The attempts were uniformly unsuccessful and the present account is concerned chiefly with the preparation and chemistry of the simple thiazolines such as (II) and (VII) which were involved.

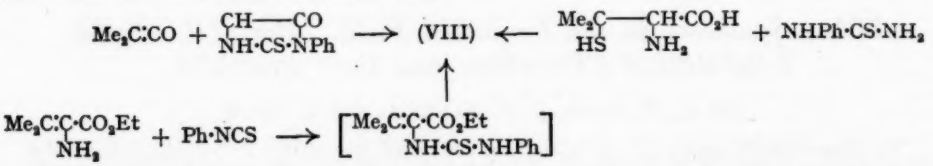
$CO_2Me{\cdot}CH{\cdot}N$ / $Me_2C{\cdot}S{\cdot}C{-}CH{\cdot}NH{\cdot}CO{\cdot}R$; CO_2Et — (I.)



After unsatisfactory efforts to induce penicillamine to react smoothly with thiocarbonyl chloride penicillamine ethyl ester and carbon disulphide had been shown to afford the 2-mercapto-thiazoline (II; R = Et) (Bentley, Catch, Cook, Heilbron, and Shaw, *CPS.* 267; " The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 466). In a similar manner there was obtained the corresponding *methyl* ester (II; R = Me) which could be hydrolysed to the corresponding *carboxylic acid* (II; R = H) and on oxidation with alkaline hydrogen peroxide gave 5 : 5-*dimethylthiazolid*-2-*one*-4-*carboxylic acid* (III). The structure of this product was indicated by its esterification to (IV) which was also obtained from penicillamine methyl ester and phosgene.

Attempts to condense (II; R = H or Me) or the analogous products (III) and (IV) with compounds containing " reactive " methylene groups (*e.g.*, 2-phenyl-5-oxazolone, 3-phenyl-5-*iso*oxazolone, or 1-phenyl-3-methyl-5-pyrazolone) were abortive. Again, ethylation of (II; R = Me) afforded the corresponding *S*-ethyl derivative (V; R = Me), the structure of which was evidenced by its basic property as contrasted with the pseudo-acidic nature of the parent

ester; the *S*-ethyl compound proved however no more useful than the foregoing thiazolines in attempted condensations with reactive methylene groups, and a still more reactive thiazoline was therefore sought. The corresponding *ethyl* ester (V; R = Et), prepared similarly, reacted with aniline to give the corresponding 2-*anilinothiazoline* which on being heated afforded the *thiohydantoin* derivative (VIII). The structure of the last compound was established by its synthesis from acetone and 1-phenyl-2-thiohydantoin; it was also obtained by interaction of ethyl α-amino-ββ-dimethylacrylate and phenyl *iso*thiocyanate (cf. the preparation of the corresponding hydantoin using phenyl *iso*cyanate; Bouveault and Wahl, *Bull. Soc. chim.*, 1901, [iii], **25**, 913), or of penicillamine and of *N*-phenylthiourea [with phenyl *iso*thiocyanate penicillamine ethyl ester yielded *N*-phenylthioureidopenicillamine ethyl ester, which on fusion lost hydrogen sulphide and formed (VIII) (*op. cit.*, p. 948)] :

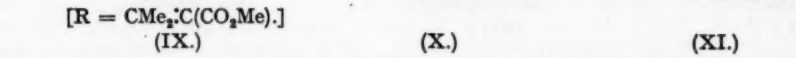


It was interesting that phenyl *iso*thiocyanate had what appeared to be a catalytic action in converting the above-mentioned anilinothiazoline into (VIII).

Heating (IV) with phosphorus pentachloride gave a comparatively stable *compound* for which the representation (VI) seems satisfactory. Several attempts to eliminate the elements of phosphorus oxychloride from the complex by treatment with sodium hydrogen carbonate, heating to 90° in a high vacuum, or chromatography on alumina resulted only in the phosphorylated compound being recovered unchanged. Efforts were then made to prepare the desired chlorothiazoline by treating the thiazolidone (IV) with phosphorus trichloride or thionyl chloride; these reagents were however without effect. Phosphorus oxychloride at 140° afforded a halogen-free oil, whilst stannic chloride gave a tin complex; neither product was further examined. Success was achieved however by use of phosphorus oxychloride and dimethylaniline (cf. Baddiley and Topham, *J.*, 1944, 678). *Methyl* 2-*chloro*-5 : 5-*dimethyl*-Δ²-*thiazoline*-4-*carboxylate* (VII) was stable at 0°, but at room temperature slowly lost hydrogen chloride, and it reverted to the parent thiazolidone (IV) on exposure to atmospheric moisture. The structure (VII) was confirmed in that heating the compound with aniline afforded the thiohydantoin derivative (VIII) which was not obtainable from (IV).

The chlorothiazoline (VII) was treated under a variety of conditions with the sodium, potassium, lithium, or magnesium derivatives of ethyl malonate, acetoacetate, hexo- or phenylacet-amidomalonate, or hexoamidoacetate, but the desired condensation products were not detected. In some of these experiments, however, products of another kind were obtained.

For example, heating the chlorothiazoline under reflux with ethyl sodioacetoacetate in a hydrocarbon diluent gave a high-melting solid which on the basis of composition and molecular weight is regarded as the iso*thiocyanurate* (IX). This compound was obtained in small yield when attempting to condense the chlorothiazoline with other compounds such as hydantoin.



[R = $CMe_2{:}C(CO_2Me)$.]

(IX.) (X.) (XI.)

The action of two equivalents of ethyl potassiohexoamidomalonate on the chlorothiazoline led to the formation of a halogen-free oil which was probably the monomeric iso*thiocyanate* (X). The compound possessed the typical mustard-oil odour and reacted with aniline to form the thiohydantoin derivative (VIII). Clearly the chlorothiazoline resembled a vinyl chloride in its reluctance to condense with alkali-metal derivatives. Reactions, when they did occur, indicated ready ring-scission; indeed, the changes observed may be represented as proceeding through the thiocarbamyl chloride (XI), which satisfactorily accounts for the ready evolution of hydrogen chloride, and the formation of (IX) and (X).

Experimental.

2-*Mercapto*-5 : 5-*dimethylthiazoline*-2-*carboxylic Acid*.—Penicillamine methyl ester hydrochloride (20 g.) was treated with aqueous sodium hydrogen carbonate, the free base extracted by chloroform (3 × 100 c.c.), and the solvent removed *in vacuo*. The residue was heated under gentle reflux with

carbon disulphide (140 c.c.) and ethanol (300 c.c.) for 2 hours. The solution was evaporated *in vacuo* to *ca.* 50 c.c., hot water (50 c.c.) added, and the filtrate cooled. *Methyl 2-mercapto-5 : 5-dimethylthiazoline-4-carboxylate* (15 g.) crystallised, and was recrystallised from ethanol–water, whence it formed colourless needles, m. p. 106—107° (Found : C, 41·05; H, 5·6; N, 6·3. $C_7H_{11}O_2NS_2$ requires C, 41·0; H, 5·4; N, 6·8%). The preceding compound (0·5 g.) was heated under reflux for 1 hour with 2N-hydrochloric acid (20 c.c.), and the solution evaporated to dryness; the residue, consisting of *2-mercapto-5 : 5-dimethylthiazoline-4-carboxylic acid*, crystallised from chloroform–light petroleum in needles, m. p. 145° (yield, 0·4 g.) (Found : C, 37·45; H, 4·7; N, 7·5. $C_6H_9O_2NS_2$ requires C, 37·65; H, 4·75; N, 7·2%).

5 : 5-Dimethylthiazolid-2-one-2-carboxylic Acid.—The above acid (2·66 g.) in N-potassium hydroxide (63 c.c.) was treated with 3% aqueous hydrogen peroxide (73 c.c.), whereupon the temperature quickly rose to 50° and began to drop after 20 minutes. The solution was evaporated to dryness *in vacuo*, and the residue extracted with ethyl acetate (3 × 5 c.c.). The extract was added to warm light petroleum, and, on cooling, colourless needles of *5 : 5-dimethylthiazolid-2-one-4-carboxylic acid* (1·6 g.) were obtained and recrystallised in similar manner; the acid had m. p. 180° (Found : C, 41·1; H, 5·1; N, 7·7. $C_6H_9O_3NS$ requires C, 41·1; H, 5·15; N, 8·0%). The same compound was obtained by similar oxidation–hydrolysis of the methyl and ethyl esters of the 2-mercaptothiazoline-acid. Prepared from the acid (0·2 g.) by means of ethereal diazomethane, *methyl 5 : 5-dimethylthiazolid-2-one-4-carboxylate* crystallised from chloroform–light petroleum in needles, m. p. 82—83° (Found : C, 44·5; H, 5·9; N, 7·25. $C_7H_{11}O_3NS$ requires C, 44·4; H, 5·9; N, 7·4%). To a stirred mixture of penicillamine methyl ester hydrochloride (17 g.), water (150 c.c.), sodium hydrogen carbonate (21·5 g.), and chloroform (100 c.c.), a 20% solution of carbonyl chloride in toluene (50 c.c.) was added slowly. The chloroform layer was washed with water and evaporated. From chloroform–light petroleum, methyl 5 : 5-dimethylthiazolid-2-one-4-carboxylate (12·7 g.) formed needles, m. p. 82°, identical with the compound obtained previously.

Ethyl 5 : 5-Dimethylthiazoline-4-carboxylates.—Ethyl 2-mercapto-5 : 5-dimethylthiazoline-4-carboxylate (10 g.) in ice-cold water (39 c.c.) containing sodium hydroxide (1·82 g.) was shaken mechanically overnight with ethyl sulphate (7 g.). The oil was taken up in ether and distilled *in vacuo*. *Ethyl 2-ethylthio-5 : 5-dimethylthiazoline-4-carboxylate* (yield, 6 g.) is a heavy oil, b. p. 122—123°/5 mm. (Found : C, 48·7; H, 7·2; N, 5·35. $C_{10}H_{17}O_2NS_2$ requires C, 48·6; H, 6·9; N, 5·55%). It (0·73 g.) was heated with aniline (0·28 g.) at 90—95° for 2 hours, ethanethiol being evolved. On cooling, the product slowly crystallised and was recrystallised from ethanol–water, to afford *ethyl 2-anilino-5 : 5-dimethylthiazoline-4-carboxylate* (0·8 g.) as needles, m. p. 125—126° (Found : C, 60·5; H, 6·6; N, 10·5. $C_{14}H_{18}O_2N_2S$ requires C, 60·4; H, 6·5; N, 10·1%). This anilino-compound (0·28 g.) was heated to 120—130° for 30 minutes; it melted and resolidified. Crystallisation from ethanol gave long needles of *3-phenyl-5-isopropylidene-2-thiohydantoin* (0·2 g.), m. p. 254—257° (decomp.) [Found : C, 62·3; H, 5·35; N, 11·9%; *M* (cryoscopic in camphor), 250. $C_{12}H_{12}ON_2S$ requires C, 62·1; H, 5·2; N, 12·0%; *M*, 232].

Other Syntheses of 3-Phenyl-5-isopropylidene-2-thiohydantoin.—(*a*) 1-Phenyl-2-thiohydantoin (Marckwald, Neumark, and Stelzner, *Ber.*, 1891, **24**, 3278) (2 g.) in dry pyridine (2·3 c.c.) was treated with acetone (1 c.c.), followed by piperidine (1·7 c.c.). The mixture was heated under reflux for 5 minutes and poured into water (50 c.c.). The filtrate was acidified to give the *iso*propylidene compound (2·1 g.), m. p. 254—257° (decomp.), identical (mixed m. p.) with the material described above.

(*b*) Ethyl α-amino-ββ-dimethylacrylate (0·18 g.) in ethanol (0·5 c.c.) was treated with phenyl *iso*thiocyanate (0·17 g.) in ethanol (0·5 c.c.). After seeding, long needles of the *iso*propylidene compound crystallised, m. p. 254—257° (decomp.) (0·27 g.).

(*c*) Penicillamine hydrochloride (0·93 g.) and *N*-phenylthiourea (Hugershoff, *Ber.*, 1899, **32**, 3659) (0·76 g.) were heated together at 110° for 1 hour. The melt resolidified. The product crystallised from ethanol in long needles of the *iso*propylidenethiohydantoin (1 g.), m. p. 254—257° decomp.).

(*d*) Ethyl 2-anilino-5 : 5-dimethylthiazoline-4-carboxylate (0·05 g.) in ethanol (3 c.c.) was treated with phenyl *iso*thiocyanate (0·045 g.). After 1 hour the *iso*propylidenethiohydantoin (0·04 g.), m. p. 254—257° (decomp.), had separated.

Methyl 2-Chloro-5 : 5-dimethylthiazoline-4-carboxylate.—A mixture of methyl 5 : 5-dimethylthiazolid-2-one-4-carboxylate (0·3 g.) and phosphorus pentachloride (0·4 g.) was heated at 100° for 55 minutes, and the product extracted with ether. The phosphorus chloride *derivative* (VI) (0·2 g.) crystallised from acetone–water at 0° as lustrous plates, m. p. 104° (Found : C, 23·3; H, 3·2; N, 4·3. $C_7H_{10}O_2NCl_4SP$ requires C, 23·3; H, 2·8; N, 3·9%). The thiazolidone (0·6 g.) and phosphorus oxychloride (5 c.c.) were heated together in a sealed tube at 140° for 3 hours, and the resultant mixture was distilled to afford a colourless pleasant-smelling *oil* (Cl and P absent), b. p. 175°/0·003 mm. [Found : C, 49·1; H, 5·75. $C_7H_{10}O_2NS$ (?) requires C, 48·8; H, 5·8%]. A solution of the thiazolidone (18 g.) in dimethylaniline (36 c.c.) and phosphorus oxychloride (72 c.c.) was heated under reflux for 3 hours. The excess of oxychloride was removed *in vacuo* as completely as possible, the dark viscous residue, diluted with some chloroform, was poured slowly on crushed ice, and the mixture stirred for 5 minutes. The product was extracted with ether (2 × 100 c.c.) which was then washed with ice-cold water (4 × 15 c.c.), dried (Na_2SO_4), and distilled, eventually under reduced pressure, to yield *methyl 2-chloro-5 : 5-dimethyl-Δ²-thiazoline-4-carboxylate* as an almost colourless oil, b. p. 90/4 mm. (Found : C, 40·5; H, 4·9. $C_7H_{10}O_2NClS$ requires C, 40·5; H, 4·8%). This oil appeared to be stable indefinitely at 0° in a sealed tube; at room temperature hydrogen chloride was slowly evolved. On exposure to atmospheric moisture, the oil gradually set to a crystalline mass, m. p. 84—85° alone or on admixture with methyl 5 : 5-dimethylthiazolid-2-one-4-carboxylate. Heating the 2-chlorothiazoline (50 mg.) with aniline (40 mg.) at 115—120° for 1·5 hours afforded, after crystallisation from ethanol, long silky needles, m. p. 252—256°, recognised as 3-phenyl-5-*iso*propylidene-2-thiohydantoin (see above).

Condensations attempted with the 2-Chlorothiazoline.—Ethyl acetoacetate (0·64 g.) was added to powdered sodium (0·11 g.) in dry benzene (5 c.c.), and the mixture was heated under reflux to complete the reaction. After cooling, methyl 2-chloro-5 : 5-dimethylthiazoline-4-carboxylate (1·0 g.) was added, and the mixture heated under reflux once more for 20 hours. Sodium chloride was removed and the filtrate evaporated to give a yellow residue which was washed with cold methanol. Recrystallisation from ethanol provided very pale yellow prisms, m. p. 206—208°, of the *isothiocyanurate* [2 : 4 : 6-*tri*-

thio-1 : 3 : 5-*tri*-(1-*carbomethoxyisobut*-1-*enyl*)*hexahydro*-1 : 3 : 5-*triazine*] (IX) [Found : C, 49·4; H, 5·4; N, 8·0%; *M* (cryoscopic in camphor), 450. $C_{21}H_{27}O_6N_3S_3$ requires C, 49·1; H, 5·3; N, 8·2%; *M*, 513].

A mixture of anhydrous sodium acetate (0·1 g.), hydantoin (0·1 g.), and the 2-chlorothiazoline (0·2 g.) was heated in glacial acetic acid (4 c.c.) at 100° for 24 hours and then evaporated *in vacuo*. By extraction of the residue with ether, pale yellow prisms were obtained and identified as the above *iso*thiocyanurate by mixed m. p.

Ethyl *n*-hexoamidoacetate (1 g.) (*op. cit.*) in ether was treated with ethereal triphenylmethylsodium (1 equiv.), followed by the 2-chlorothiazoline (1 g.). After 24 hours sodium chloride was removed and the filtrate distilled, eventually in a high vacuum at 100°. Some triphenylmethane sublimed and a crystalline residue was left in the retort. Recrystallisation of the residue from ethanol gave pale yellow prisms which did not depress the m. p. of the above *iso*thiocyanurate, and there remained a little ethanol-insoluble material, m. p. *ca.* 220°, which was probably *p*-benzhydryltetraphenylmethane (see below).

A solution of ethyl *n*-hexoamidomalonate (1·35 g.) in ether was treated with ethereal triphenylmethylsodium (1 equiv.), followed by the 2-chlorothiazoline (1 g.). After 24 hours the ether was washed with water and evaporated, and the residue fractionally crystallised from aqueous ethanol and ether–light petroleum, to yield triphenylmethane, m. p. 74—75°. An attempt to isolate a reaction product by distilling the mother-liquors in a high vacuum led to the isolation of hardly-volatile *p*-benzhydryltetraphenylmethane which formed very pale yellow plates, m. p. 223—224°, from benzene–methanol (Found : C, 93·3; H, 6·3. Calc. for $C_{38}H_{30}$: C, 93·8; H, 6·2%). Tschitschibabin (*Ber.*, 1908, **41**, 2427) records m. p. 227° for this self-condensation product of triphenylmethyl.

A mixture of ethyl *n*-hexoamidoacetate (1 g.), the 2-chlorothiazoline (2 g.), and benzene (10 c.c.) was added to powdered potassium (0·195 g.) under light petroleum (b. p. 60—80°). After 7 days at room temperature the mixture was filtered and concentrated *in vacuo* to crystallisation. From benzene–light petroleum a halogen-free *product* (unidentified) separated as pale yellow prisms, m. p. 180—181° [Found : C, 48·3; H, 5·8%; *M* (cryoscopic in camphor), 168. $C_7H_{10}O_2NS$ requires C, 48·8; H, 5·8%; *M*, 172]. The same substance (0·1 g.), m. p. 183° (a mixture showed no depression), was isolated after the 2-chlorothiazoline (1 g.) had been boiled under reflux for 14 hours with an ethereal suspension of the derivative formed from ethyl *n*-hexoamidomalonate (1·35 g., 1 equiv.) and powdered potassium (0·19 g.).

A potassium derivative, formed by treating ethyl *n*-hexoamidomalonate (2·7 g.) with powdered potassium (0·38 g.) under ether (15 c.c.), was heated under reflux with the 2-chlorothiazoline (1 g., 0·5 equiv.) in benzene (15 c.c.) for 16 hours. The mixture was washed with water (5 × 25 c.c.), filtered, dried (Na_2SO_4), concentrated *in vacuo*, and treated with light petroleum, whereupon unchanged hexoamidomalonate crystallised. Distillation of the filtrate yielded a halogen-free, mobile, pale yellow oil, b. p. 100°/2 mm., which smelled of mustard oil and reacted overnight with ethereal aniline to form long needles, m. p. 252°, of 3-phenyl-5-*iso*propylidene-2-thiohydantoin (see above).

Grateful acknowledgment is made of the award of a William Gilles Research Fellowship (to J. A. E.) and of a Senior Research Grant from the Medical Research Council (to G. S.) which made possible participation in the above work, and of assistance from the Therapeutic Research Corporation of Great Britain, Ltd. The authors thank Sir Ian Heilbron, D.S.O., F.R.S., for his interest and advice.

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NOTES.

Some Reactions of 3 : 5-*Di-iodoanisaldehyde.* By J. H. WILKINSON.

PRESSURE of other work having led to the abandonment of the project of synthesising sulphonic acid analogues of 3 : 5-di-iodotyrosine, it is considered desirable to report the results obtained. 3 : 5-*Di-iodoanisaldehyde* was prepared from 3 : 5-di-iodo-4-hydroxybenzaldehyde (Paal and Mohr, *Ber.*, 1895, **28**, 2407), and was reduced by the Meerwein–Pondorff method to 3 : 5-*di-iodo*-p-*methoxyphenyl alcohol*. With nitromethane the aldehyde gave 3 : 5-*di-iodo*-β-*nitro*-4-*methoxystyrene*, but it failed to react with sodium hydrogen sulphite.

The bisulphite compounds of anisaldehyde and phenylacetaldehyde reacted with ammonia (cf. McIlwain, *J.*, 1941, 75) to give the sulphonic acid analogues of *p*-methoxyphenylglycine and phenylalanine respectively.

Experimental.—(Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.)

3 : 5-*Di-iodoanisaldehyde dimethyl acetal.* 3 : 5-Di-iodo-4-hydroxybenzaldehyde (20 g.) was partly dissolved and partly suspended in a mixture of methanol (100 c.c.) and methyl sulphate (16 c.c.), cooled in an ice-bath. A solution of sodium hydroxide (8 g.) in water (15 c.c.) was added in one instalment and the mixture stirred. The temperature rose to about 70°. The solution was cooled and diluted with water whereupon the *acetal* (11·45 g.) separated. It crystallised from light petroleum (b. p. 40—60°) in pale yellow rhombs, m. p. 66° (Found : C, 27·9; H, 2·4; I, 59·8. $C_{10}H_{12}O_3I_2$ requires C, 27·7; H, 2·75; I, 58·6%). Acidification of the alkaline liquors precipitated unreacted 3 : 5-di-iodo-4-hydroxybenzaldehyde (7·3 g.).

3 : 5-*Di-iodoanisaldehyde.* The dimethyl acetal (5·9 g.) was heated under reflux with 2N-hydrochloric acid (25 c.c.) for 5 minutes. The solid was collected (5·29 g.) and crystallised from benzene, the *aldehyde* being obtained in buff-coloured needles, m. p. 124°, sparingly soluble in light petroleum (Found : C, 24·4; H, 1·8; I, 65·5. $C_8H_6O_3I_2$ requires C, 24·7; H, 1·6; I, 65·4%). When heated above its m. p., it underwent rapid oxidation to 3 : 5-di-iodo-*p*-anisic acid, m. p. 253° (Wheeler and

Liddle, *Amer. Chem. J.*, 1909, **42**, 441, report m. p. 255—256°). The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous dioxan in orange-red prisms, m. p. 270° (decomp.) (Found: N, 9·5. $C_{14}H_{10}O_5N_4I_2$ requires N, 9·85%). It was sparingly soluble in most organic solvents.

Attempted preparation of α-amino-α-(3 : 5-di-iodo-4-methoxyphenyl)methanesulphonic acid. 3 : 5-Di-iodoanisaldehyde (1 g.) was suspended in alcohol (5 c.c.) at 70° and treated with a solution of sodium hydrogen sulphite (0·3 g.; 20% excess). The mixture was shaken mechanically for 2 hours, and the temperature kept at 70°. Water (10 c.c.) was added to the cooled mixture and the unreacted aldehyde (0·95 g.) was recovered by filtration.

3 : 5-*Di-iodoanisyl alcohol.* 3 : 5-Di-iodoanisaldehyde (3·88 g.) was added to a solution of aluminium *iso*propoxide (0·4 g.) in anhydrous *iso*propyl alcohol (80 c.c.), the mixture heated under reflux for 2 hours and the acetone, produced in the reaction, then removed by distillation. After 7 hours no more acetone could be detected in the distillate by the 2 : 4-dinitrophenylhydrazine test. The solvent was removed and the cooled residue treated with 2N-hydrochloric acid (25 c.c.). The solid was collected, washed with 2N-hydrochloric acid and water, and dried ($CaCl_2$). Yield: 3·81 g. (98%). 3 : 5-Di-iodoanisyl alcohol crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 82°, highly soluble in alcohol and benzene (Found: C, 24·8; H 2·2; I 65·2. $C_8H_8O_2I_2$ requires C, 24·6; H, 2·05; I, 65·2%).

3 : 5-*Di-iodo-4-methoxybenzyl chloride.* The alcohol (1·7 g.) was dissolved in anhydrous benzene (5 c.c.) and heated under reflux with thionyl chloride (1·5 c.c.) for 1 hour. The excess of reagent and solvent were removed and the residue was dried at 50°/15 mm. Yield: 1·66 g. (93%). The *product* crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 74—75°, highly soluble in most organic solvents (Found: C, 23·9; H, 1·8. $C_8H_7OClI_2$ requires C, 23·5; H, 1·7%). An attempt to condense this with ethyl malonate in the presence of 1 equivalent of sodium ethoxide failed.

3 : 5-*Di-iodo-β-nitro-4-methoxystyrene.* 3 : 5-Di-iodoanisaldehyde (4 g.) was dissolved in alcohol (30 c.c.) and treated with nitromethane (0·62 g.). The mixture was cooled to 0° and sodium hydroxide (2·6 c.c., 5N. in 50% alcohol) was added dropwise with mechanical stirring, the temperature being kept below 10°. After 15 minutes, the mixture was diluted with ice-water and filtered from unchanged di-iodoanisaldehyde. The filtrate was added to 2N-hydrochloric acid (25 c.c.) and the solid collected. Yield: 1·8 g. (41%). It crystallised from 20% alcohol in pale yellow needles, m. p. 149° (Found: C, 25·1; H, 1·75; N, 3·3; I, 58·5. $C_9H_7O_2NI_2$ requires C, 25·1; H, 1·6; N, 3·25; I, 58·9%). This *nitrostyrene* (0·74 g.) in dioxan solution (6 c.c.) was added to 1·5M-sodium hydrogen sulphite (2 c.c.) and the solution shaken mechanically for 48 hours. Water (10 c.c.) was added to precipitate the unreacted nitrostyrene (0·41 g.) and the mixture centrifuged. The supernatant liquid was evaporated; the residue was dissolved in alcohol and filtered from a little sodium hydrogen sulphite. The alcohol was removed from the filtrate, but the highly water-soluble residue, believed to consist of sodium 2-nitro-1-(3 : 5-di-iodo-4-methoxyphenyl)ethane-1-sulphonate, could not be induced to crystallise.

α-Amino-α-p-methoxyphenylmethanesulphonic acid. The bisulphite compound [from distilled anisaldehyde (5·44 g.) and sodium hydrogen sulphite (4·16 g.)] was treated at 20° with ammonia (20 c.c., *d* 0·88) in a sealed tube for 1½ hours, followed by ½ hour at 50°. The mixture was cooled, filtered, and acidified at 0° with 10N-sulphuric acid. The solid which separated was collected, washed with 50% alcohol, alcohol, and ether, and dried at 20°/15 mm. Yield: 2·1 g. (24%). The addition of alcohol to the filtrate precipitated a further 3·8 g. (44%) but this was contaminated with ammonium sulphate. The main *product* was crystallised from water at a temperature not exceeding 70°—it separated in highly soluble colourless needles, m. p. 123° (decomp.) (Found: N, 6·55; S, 15·0. $C_9H_{11}O_4NS$ requires N, 6·45; S, 14·75%).

α-Amino-β-phenylethanesulphonic acid was prepared in a similar manner from redistilled phenylacetaldehyde. The product was sparingly soluble in water and on heating to promote solution, the compound decomposed to give a highly soluble substance, which appeared to be the ammonium salt of the α-hydroxy-acid. Purification of the required compound was therefore effected by successive trituration with water, alcohol, and ether. The product was a colourless powder, m. p. 147° (decomp.) (Found: N, 6·9; S, 15·3. $C_8H_{11}O_3NS$ requires N, 6·96; S, 15·9%).

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The Diacrylate and Dimethacrylate of But-2-yne-1 : 4-diol. By L. F. Wiggins and D. J. C. Wood.

Several esters and other derivatives of but-2-yne-1 : 4-diol have been described by Johnson (*J.*, 1946, 1009) and other aspects of the chemistry of this most interesting compound are recorded by Reppe (see "New Technical Applications of Acetylene", H.M. Stationery Office, 1946). *But-2-yne-1 : 4-diol diacrylate* and the corresponding *dimethacrylate* were prepared from the alcohol and the requisite acid chloride in the presence of sodium hydroxide, and the product was extracted with ether. The diacrylate was a liquid and the dimethacrylate a crystalline solid of low melting point, both compounds being purified by distillation under reduced pressure. Both esters polymerised very readily, so much so that their isolation in good yield was difficult. Attempts to polymerise the dimethacrylate with poly(methyl methacrylate) according to the current practice in dental prosthetics were unsuccessful. Poly(methyl methacrylate) did not apparently dissolve in the monomeric butynediol dimethacrylate.

But-2-yne-1 : 4-diol Diacrylate.—Butynediol, m. p. 54°, (1 g.) was dissolved in sodium hydroxide solution (5N.; 8 c.c.), and acrylyl chloride (2 c.c.) added in small portions with shaking and cooling in an ice-bath. The ester separated as an oil, which was extracted with ether, the extract was dried ($MgSO_4$), and the solvent evaporated under reduced pressure, copper powder (0·5 g.) being added as a polymerisation inhibitor. *But-2-yne-1 : 4-diol diacrylate* (1·4 g.) distilled at 106—111° (bath temp.)/0·1 mm. as a colourless oil (0·4 g., 18%), n_D^{17} 1·4871 (Found: C, 62·0; H, 5·3. $C_{10}H_{10}O_4$ requires C, 61·9; H,

5·2%). The remainder of the crude product polymerised to a colourless gel before distillation was completed.

But-2-yne-1 : 4-diol Dimethacrylate.—Butynediol (2 g.) was dissolved in sodium hydroxide solution (5N.; 20 c.c.) and methacrylyl chloride (5·5 c.c.) added in small portions with shaking and cooling in an ice-bath. The oil which separated was extracted with ether, the extract was washed with water and dried ($MgSO_4$), and the ether was removed under reduced pressure in a stream of nitrogen and in the presence of copper powder (0·5 g.). The *but-2-yne-1 : 4-diol dimethacrylate* was distilled in nitrogen at 116—120° (bath temp.)/0·05 mm. and was obtained as a colourless oil (2·8 g.; 54%), n_D^{18} 1·4846, soluble in alcohol, benzene, chloroform, light petroleum, and ethyl acetate (Found: C, 64·8; H, 6·5. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%). On refrigeration the ester crystallised completely. It was recrystallised with difficulty from aqueous alcohol and then had m. p. 28·5—29°. The ester polymerised very readily; it could be kept in the monomeric state for 1—2 weeks only, even at 0° in the presence of copper powder. Heating at 90—100° caused rapid decomposition accompanied by considerable increase in viscosity, copious evolution of fumes, and much charring. At 70—80°, however, with the addition of a little benzoyl peroxide, the ester remained fluid and apparently unchanged for a few minutes, and then was suddenly transformed into a colourless gel. Further heating gradually produced a clear, hard, very brittle resin, which was insoluble in organic solvents (*e.g.*, chloroform), and was not appreciably attacked by boiling concentrated nitric acid or aqua regia, but it slowly disintegrated in hot concentrated sodium hydroxide.

When the ester was heated in an atmosphere of nitrogen, polymerisation was appreciably retarded. Without this precaution it was extremely difficult to distil it, but even in the presence of nitrogen a second distillation resulted in only about half being recovered as the monomer.

The monomer showed no solvent action on granular poly(methyl methacrylate) during 20 minutes at room temperature. When warmed in a water-bath at 50° for about 10 minutes the mixture attained a doughlike consistency and polymerisation of this product at 100° gave a hard resin, but in this material the original poly(methyl methacrylate) granules were easily visible and the surrounding medium clearly consisted only of butynediol dimethacrylate which had polymerised without dissolving the granules.—THE A.E. HILLS LABORATORIES, THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15. [*Received, May 10th*, 1949.]

The Interaction of the Silver Salts of Optically Active Acids with Bromine. By F. BELL and I. F. B. SMYTH.

IN view of the publication of a paper by Arnold and Morgan (*J. Amer. Chem. Soc.*, 1948, **70**, 4248) and of a letter by Arcus, Campbell, and Kenyon (*Nature*, 1949, **163**, 287) on this topic, results previously obtained by us are briefly communicated.

Silver (+)- and (−)-α-ethylhexoates in carbon tetrachloride suspension were converted by the action of bromine into 3-bromoheptane, which in all experiments proved to be optically inactive. This result agrees with that of Arnold and Morgan but is more conclusive in that the (+)- and (−)-ethylhexoic acids used were almost optically pure and, in the final experiments, the time of heating was considerably less.

Next, silver (+)- and (−)-diphenylsuccinates in carbon tetrachloride suspension were converted by the action of bromine into 1 : 2-dibromo-1 : 2-diphenylethane. The material isolated was mainly the relatively insoluble *meso*dibromo-derivative, m. p. 237°; the remainder (about 15%) was slightly impure inactive dibromodiphenylethane, m. p. 101—105° (Wislicenus and Seeler, *Ber.*, 1895, **28**, 2693, give m. p. 237° and 110° for the two isomers).

Silver (+)- and (−)-benzylethylacetates (α-benzylbutyrates) were similarly converted into 2-bromo-1-phenylbutane. The product from the (−)-salt was completely inactive but that from the (+)-salt showed the very small specific rotation of −2·8°. The salts were decomposed under apparently identical conditions and the reason for this difference is obscure.

Although the results of the present investigations might have been held to favour a free-radical mechanism for the replacement, this conclusion is entirely negatived by the work of Arcus, Campbell, and Kenyon, to whose views we subscribe.

Experimental.—Silver (+)- and (−)-α-Ethylhexoates.—Ethylhexoic acid was prepared and resolved by the method of Kenyon and Platt (*J.*, 1939, 633). Silver salts were prepared from acids of $[\alpha]_{5461}$ +9·79° and −9·9°. Many decomposition experiments were made and the following description represents the mildest conditions employed. Silver (+)-α-ethylhexoate (15 g.), dried *in vacuo* over phosphoric oxide and finely ground, was suspended in carbon tetrachloride (150 ml.) and treated with a solution of bromine (8 g.) in carbon tetrachloride (30 ml.) with external cooling. The mixture was heated under reflux for 15 minutes on the water-bath, filtered, and shaken with sodium hydroxide and water. Distillation yielded 3-bromo-*n*-heptane (4 g.), b. p. 51—54°/17 mm., n_D^{20} 1·4511 (Dillon and Lucas, *J. Amer. Chem. Soc.*, 1928, **50**, 1713, give b. p. 84—85°/74 mm., n_D^{20} 1·4507). The product was devoid of optical activity.

Silver (+)- and (−)-Diphenylsuccinates.—Diphenylsuccinic acid was resolved by crystallisation of the quinidine salt from 50% aqueous alcohol. Ten crystallisations yielded (+)-diphenylsuccinic acid, which on a further crystallisation from aqueous acetic acid had $[\alpha]_{5461}^{20}$ +351° (*c*, 1·0 in alcohol, *l* = 1).

Kolin (Ph.D. Thesis, Queen's University, Belfast, 1945) has briefly described the interaction of optically inactive silver diphenylsuccinate with bromine. His procedure and the following were applied to the optically active salts with essentially similar results.

Silver (+)-diphenylsuccinate (10·8 g.) was heated under reflux with bromine in carbon tetrachloride for 45 minutes. After filtration and washing with sodium hydroxide and water, the carbon tetrachloride was distilled, leaving a yellow pasty residue. Extraction with alcohol and recrystallisation of the soluble portion yielded a very small quantity of 1 : 2-dibromo-1 : 2-diphenylethane, m. p. 101—105°, which was optically inactive. Recrystallisation of the alcohol-insoluble portion from xylene gave the high-melting isomer, m. p. 237°, which is the principal product of the reaction.

Silver (+)- and (−)-Benzylethylacetates.—Benzylethylacetic acid was prepared by the reduction of phenylangelic acid (Baeyer and Jackson, *Ber.*, 1880, **13**, 118) and resolved by use of (−)-menthylamine (Pickard and Yates, *J.*, 1909, **95**, 1018). Silver (+)-benzylethylacetate (19 g.), obtained from the acid of $[\alpha]_{5461}$ +30·9°, was treated with bromine in carbon tetrachloride and heated under reflux for ½ hour. After working up as before, 3 g. of 2-bromo-1-phenylbutane were obtained as a pale pink liquid, b. p. 110—115°/16 mm., n_D^{18} 1·5447 (Carter, *J. Biol. Chem.*, 1935, **108**, 619, records b. p. 98—99°/1 mm., n_D^{20} 1·5393). It had $[\alpha]_{5461}$ −2·85° (*c*, 14·37 in alcohol; *l* = 1). Treatment of silver (−)-benzylethylacetate in a precisely similar manner gave optically inactive 2-bromo-1-phenylbutane.

A decision to apply this method to optically active diphenic acids was abandoned when it was found that silver diphenate would not react smoothly with bromine to give 2 : 2′-dibromodiphenyl.

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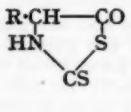
The Action of Thionyl Chloride on Some Esters of N-Dithiocarboxyamino-acids.

By Charles E. Dalgliesh.

The revival of interest in the Leuchs polymerisation of anhydrocarboxyamino-acids (Leuchs *et al.*, *Ber.*, 1906, **39**, 857; 1907, **40**, 3235; 1908, **41**, 1721; Woodward and Schramm, *J. Amer. Chem. Soc.*, 1947, **69**, 1551) suggested the investigation of dithio-compounds of type (I) which might also be expected to give polypeptides. By analogy such a compound should be formed on treatment of a *N*-dithiocarbalkoxyamino-acid $CS_2R''\cdot NH\cdot CHR'\cdot CO_2H$ (II), with thionyl chloride, followed by cyclisation.



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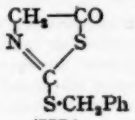

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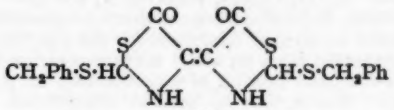

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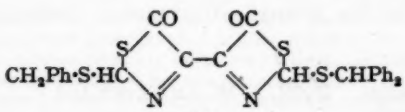

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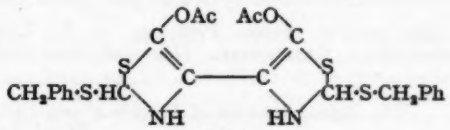


(VI.)

On treatment of *N*-dithiocarbobenzyloxyglycine (II; R′ = H, R″ = CH_2Ph) (Cook, Harris, Heilbron, and Shaw, *J.*, 1948, 1056) with thionyl chloride, the mixture became deep red, and readily gave brilliant scarlet needles in good yield. These contained no chlorine, no reactive methylene group, and could not be acetylated. Treatment of (II; R′ = H, R″ = CH_2Ph) in ether–dioxan with phosphorus tribromide was shown by Cook *et al.* to give the colourless hydrobromide of 2-benzylthiothiazolone (III). The striking colour of our product showed clearly that compounds of types (I; R = H) and (III) were not present, whilst the ready and rapid formation made it unlikely that very deep-seated changes had occurred. Molecular-weight determinations indicated that two benzylthiothiazolone residues were present, and the compound is suggested as possibly having either the indigo-like structure (IV) or, more probably, the dehydroindigo-like structure (V). Either structure (IV) or (V) would explain the intense colour; whereas (III) and (IV) have the same elemental composition, the formation of (V) would involve oxidation. Treatment with sodium dithionite (hydrosulphite) caused decomposition and the liberation of toluene-*ω*-thiol due to instability to alkali, but the compound could be reductively acetylated to give a product agreeing in analytical values with the *diacetate* (VI), which might be expected to be formed from either (IV) or (V).

Products of types (IV) and (V) obviously could not be formed from amino-acids other than glycine, as the carbon atoms required to carry the indigoid or dehydroindigoid double bonds would carry a substituent. Moreover an analogue of (V) could not be formed from the corresponding sarcosine derivative, nor could an analogue of (IV) if, as seems probable from the evidence below, the reaction takes place *via* the thiazolone type of structure (III). In agreement with this, treatment of *N*-dithiocarbobenzyloxy-DL-phenylalanine with thionyl chloride gave only a brown gum from which was isolated in low yield pale yellow needles of a compound obviously quite different in type from the highly coloured glycine derivative, nor was any highly coloured material obtained by the action of thionyl chloride on *N*-dithiocarbobenzyloxysarcosine. On the other hand very vigorous reaction occurred when thionyl chloride was added to *N*-dithiocarbethoxyglycine, $EtO_2C\cdot S\cdot CS\cdot NH\cdot CH_2\cdot COOH$ (Cook *et al.*, *loc. cit.*), to yield a highly coloured material, and a similar product was obtained by the action of thionyl chloride on *N*-dithiocarbo-*m*-nitrophenacyloxyglycine, $m\text{-}NO_2\cdot C_6H_4\cdot CO\cdot CH_2\cdot S\cdot CS\cdot NH\cdot CH_2\cdot COOH$.

The mechanism of the reaction is obscure. When dithiocarbobenzyloxyglycine was treated with oxalyl chloride (cf. Adams and Ulich, *J. Amer. Chem. Soc.*, 1920, **42**, 599) only a yellow gum was obtained, presumably containing the hydrochloride of (III), and, as Cook *et al.* showed, the use of phosphorus tribromide gives the hydrobromide of (III). It was found that on treatment of this hydrobromide with thionyl chloride a vigorous reaction again occurred in the cold, and the product was identical with that from dithiocarbobenzyloxyglycine itself. It is therefore suggested that formation of (IV) or (V) occurs by way of the benzylthiothiazolone (III), possibly with intermediate chlorination and loss of hydrogen chloride between two molecules. An indigoid structure similar to (IV), but formed

from two glyoxaline nuclei, has been postulated by Hunter and Hlynka (*Canadian J. Res.*, 1941, **19**, *B*, 305) for a compound which they prepared.

As this is not connected with the main problem in hand further work has not been carried out, but the results are reported in view of the current interest in thiazole chemistry.

Experimental.—Thionyl chloride (10 ml.) was added to *N*-dithiocarbobenzyloxyglycine (10 g.) in a flask protected from moisture. Vigorous evolution of gas occurred and the mixture became deep red. When the initial reaction had subsided the flask was heated for 15 minutes in a water-bath at 40°, and the excess of thionyl chloride then pumped off. The dark residue was recrystallised from benzene and then from dioxan. The *product* formed glistening scarlet needles, m. p. 202° (decomp.). The purified material (3·6 g.) was dried (P_2O_5) for 4 hours at 80° in a high vacuum before analysis; the molecular weight was determined by elevation of the b. p. of benzene [Found: C, 54·4; H, 3·6; N, 6·4; S, 27·8%; *M*, 437 (mean). The dehydroindigoid formula (V), $C_{20}H_{16}O_3N_2S_4$, requires C, 54·0; H, 3·6; N, 6·3; S, 28·8%; *M*, 444. The indigoid formula (IV), $C_{20}H_{18}O_2N_2S_4$, requires C, 53·8; H, 4·0; N, 6·3; S, 28·7%; *M*, 446]. This material (0·5 g.) was reductively acetylated by boiling it for 3 hours with acetic anhydride (5 ml.), acetic acid (5 ml.), and powdered zinc. Almost colourless needles of an *acetate*, m. p. 133—135°, were obtained. These darkened somewhat on exposure to air [Found: C, 54·0; H, 4·7; N, 5·5. The diacetate (VI), $C_{24}H_{24}O_4N_2S_4$, requires C, 54·1; H, 4·5; N, 5·3%].

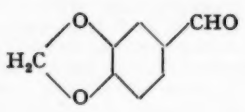
Treatment of DL-phenylalanine in alkaline solution with carbon disulphide and then benzyl chloride, according to the instructions given by Cook *et al.* for the glycine derivative, gave *N-dithiocarbobenzyloxy-DL-phenylalanine*, which could not be induced to crystallise (Found: N, 4·3. $C_{17}H_{17}O_2NS_2$ requires N, 4·2%). Similar treatment of sarcosine gave *N-dithiocarbobenzyloxysarcosine*, as colourless needles, m. p. 119—120°, from ethyl acetate–ligroin (Found: N, 5·3. $C_{11}H_{13}O_2NS_2$ requires N, 5·5%). Treatment of glycine with carbon disulphide and then *m*-nitrophenacyl bromide dissolved in dioxan gave N-*dithiocarbo*-m-*nitrophenacyloxyglycine*, m. p. 141° (decomp.) (from ethyl acetate) (Found: N, 9·0. $C_{11}H_{10}O_5N_2S_2$ requires N, 8·9%).

When *N*-dithiocarbobenzyloxy-DL-phenylalanine was treated with thionyl chloride and the excess removed as already described for the glycine analogue, a yellowish mass remained and was purified by precipitation from an ethyl acetate solution by ligroin, followed by recrystallisation. Long (2—3 cm.) straw-coloured needles of a compound, m. p. 119—120°, were obtained (Found: C, 66·7; H, 5·3; N, 5·9%). The action of thionyl chloride on *N*-dithiocarbo-*m*-nitrophenacyloxyglycine gave brick-red needles, which darkened above 180°, decomposed at 201°, and also decomposed in hot solution. *N*-Dithiocarbocarbethoxyglycine gave green irridescent needles, m. p. 218° (decomp.).

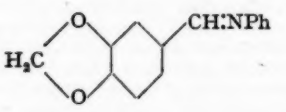
The author thanks Professor A. R. Todd, F.R.S. for his interest.—UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, May 16th*, 1949.]

The Dipole Moment of Piperonal and Piperonylideneaniline. By R. J. W. LE FÈVRE and (MISS) JEAN NORTHCOTT.

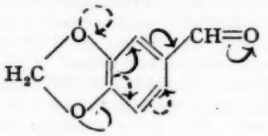
IN another connection it became of interest to ascertain whether the methylenedioxy-ring in piperonaldehyde has a significant effect on the resultant molecular polarity of molecules containing it. Accordingly the moments of piperonaldehyde and its anil were determined in benzene solution, using apparatus and techniques already described (Calderbank and Le Fèvre, *J.*, 1948, 1949).



(I.)



(II.)



(III.)

Recrystallised piperonaldehyde (from aqueous alcohol) was distilled (b. p. 142°/18 mm.) immediately before use. The anil (cf. Lorenz, *Ber.*, 1881, **14**, 792), after crystallisation from ligroin, had m. p. 65° in agreement with the literature. Experimental data and calculations are tabulated below, using symbols explained in " Dipole Moments " (Methuen, 1948, pp. 39—41):

Dielectric constants and densities.

$10^6 \times w_1$.	$\varepsilon^{25°}$.	d_4^{25}.	$a\varepsilon_2$.	β.
—	2·2725	0·87378	—	—
		Piperonaldehyde.		
3,521	—	0·87487	—	0·356
4,820	—	0·87528	—	0·357
5,219	2·3206	0·87557	9·15	0·389
6,428	2·3329	0·87589	9·40	0·376
6,931	—	0·87593	—	0·354
7,667	2·3416	0·87608$_5$	9·01	0·345
8,654	2·3512	0·87631	9·09	0·335
19,739	2·4521	0·87960	9·10	0·337
		Piperonylideneaniline.		
3,344	2·2793	0·87464	2·03	0·295
6,504	2·2856	0·87543	2·01	0·290
8,781	2·2901	0·87605	2·00	0·296
12,721	2·2987	—	2·06	—

Molecular refractions.

$10^6 \times w_1$.	d_4^{25}.	n_D^{25}.	r_{12} (c.c.).	$(R_L)_D$ c.c.
0	0·87378	1·4972 *	$0·33500_5$	—
Piperonaldehyde.				
7,667	$0·87608_5$	1·4979 *	0·33442	39·3 †
Piperonylideneaniline.				
6,504	0·87543	1·4992 *	$0·33551_5$	69·9 †

* Abbé refractometer used.

† Calc. from benzaldehyde ($R_D = 32$) or benzylideneaniline ($R_D = 62$) by adding R_O and twice $R_{Ether\text{-}O} = 38$ and 68 c.c. respectively. Conduché (*Ann. Chim. Phys.*, 1908, [viii], **13**, 94) found a mean value of 40 c.c. for piperonaldehyde in acetic acid solutions.

Results.

	m.	$\alpha\varepsilon_1$.	β.	P_T.	$[R_L]_D$.	μ_D.
Piperonaldehyde	150·13	9·15	0·356	$291·3_5$	39·3	$3·4_9$
Piperonylideneaniline	225·24	$2·02_5$	0·294	140·0	69·9	$1·8_5$

Results.

Discussion.—These appear to be the first dipole-moment determinations of compounds possessing the methylenedioxy-group. Comparisons with benzaldehyde (2·98 D.; Calderbank and Le Fèvre, this vol., p. 1462) and benzylideneaniline ($1·6_1$ D.; de Gaouck and Le Fèvre, *J.*, 1938, 741) show the values now recorded to be slightly greater in each case (by $\mu = 0·5$ and 0·3 D., respectively). Since the molecular resultant in benzaldehyde has a direction of action lying at $143\frac{1}{2}°$ to an axis set successively through carbon atoms nos. 4 and 1 and has its negative pole directed away from the *Ar*-nucleus (Coomber and Partington, *J.*, 1938, 1444), it is evident that the hetero-ring contributes a small moment in a co-operative sense.

This increment might arise from an unequality of the effects of ring strain on the $C_{Aliphatic}$–O and $C_{Aromatic}$–O link moments. Thus available data (*Trans. Faraday Soc.*, 1934, Appendix) for the polymethylene ethers $(CH_2)_nO$ ($n = 2$—5), if analysed on the simplest geometrical assumptions regarding intervalency angles and with the same H–C moment throughout, suggest that $\mu_{C\text{-}O}$ becomes greater as the ring becomes smaller. Walsh (*Ann. Reports*, 1947, 45) has noted that, for a given bond, the stretching force constant and the polarity run somewhat inversely. It may therefore be relevant that for the C–O links in dimethyl ether and ethylene oxide the former property appears as 4·53 or 4·56 and $4·43 \times 10^5$ dynes/cm., respectively (quoted by Ramsay, *Proc. Roy. Soc.*, 1947, *A*, **190**, 573).

Qualitatively, however, since piperonaldehyde undergoes halogenation and nitration in the 6-position (cf. Beilstein, "Handbuch," *XIX*, 115, for references) we prefer to ascribe the slight increase of moment observed to the mesomerism expressed by (III), which indicates graphically one way in which the C–O bond moment may be modified by the C being "aliphatic" or "aromatic."

Our thanks are due to the Research Committee of this Society for the continued loan of a standard Sullivan variable air condenser.—UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, February 28th*, 1949.]

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